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Official Title:	Multi-center, open-label, uncontrolled study to assess contraceptive efficacy and safety of Mirena during extended use beyond 5 years in women 18 to 35 years of age including a subgroup evaluation of treatment effect on heavy menstrual bleeding
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Cover page of the integrated protocol

Multi-center, open-label, uncontrolled study to assess contraceptive efficacy and safety of Mirena during extended use beyond 5 years in women 18 to 35 years of age including a subgroup evaluation of treatment effect on heavy menstrual bleeding

This protocol version is an integration of the following documents / sections:

1. **Original protocol,** Version 1.0, dated 03 AUG 2016
2. **Amendment 1** (described in Section 15.1)
   forming integrated protocol Version 2.0, dated 20 SEP 2017

1. Title page

Multi-center, open-label, uncontrolled study to assess contraceptive efficacy and safety of Mirena during extended use beyond 5 years in women 18 to 35 years of age including a subgroup evaluation of treatment effect on heavy menstrual bleeding

Short title:	Mirena Extended Trial		
Acronym:	MET		
Test drug:	Levonorgestrel BAY86-5028 / levonorgestrel-releasing intrauterine system, Mirena		
Study purpose:	Efficacy		
Clinical study phase:	3	Date:	20 SEP 2017
Registration:	Not applicable	Version no.:	2.0
Sponsor's study no.:	18649		
Sponsor:	**Bayer HealthCare Pharmaceuticals Inc.** 100 Bayer Boulevard (P.O. Box 915) Whippany NJ 07981-0915, US		
Sponsor's medical expert:	PPD Bayer HealthCare Pharmaceuticals 11 Waterview Boulevard Parsippany, NJ 07054 Phone no. PPD		

The study will be conducted in compliance with the protocol, ICH-GCP and any applicable regulatory requirements.

Signature of the sponsor's medically responsible person

The signatory agrees to the content of the final integrated clinical study protocol as presented.

Name: PPD Role: PPD

Date: PPD Signature: PPD

Signature of principal investigator

The signatory agrees to the content of the final integrated clinical study protocol as presented.

Name:

Affiliation:

Date: ..... Signature: .....

Signed copies of this signature page are stored in the sponsor's study file and in the respective center's investigator site file.

In the integrated protocol document, this page may remain unsigned.

2. Synopsis

Title	Multi-center, open-label, uncontrolled study to assess contraceptive efficacy and safety of Mirena during extended use beyond 5 years in women 18 to 35 years of age including a subgroup evaluation of treatment effect on heavy menstrual bleeding
Short title	Mirena Extended Trial
Acronym	MET
Clinical study phase	3
Study objectives	Primary objective of the study is to assess the contraceptive efficacy of Mirena beyond 5 years up to 8 years of use. Secondary objectives for the study are the assessment of menstrual blood loss (in women that had Mirena inserted for the indication heavy menstrual bleeding [HMB]) and safety. Further objectives are the population pharmacokinetic evaluation of LNG plasma concentration data and evaluation of user satisfaction.
Test drug	Mirena, levonorgestrel-releasing intrauterine system
Name of active ingredient	Levonorgestrel (LNG)
Dose	Initial release rate: 20 µg per day
Route of administration	Intrauterine
Duration of treatment	Up to 3 years (total use of the current Mirena up to 8 years)
Reference drug	None
Indication	Intrauterine contraception Treatment of heavy menstrual bleeding for women who choose to use intrauterine contraception as their method of contraception.
Diagnosis and main criteria for inclusion /exclusion	Fertile age women (18 to 35 years at the time of the screening visit) currently using a Mirena for contraception or for contraception and heavy menstrual bleeding and who have had the Mirena in situ for at least 4 years and 6 months but no longer than 5 years and are willing to continue its use for contraception or contraception and heavy menstrual bleeding for up to 8 years in total.
Study design	Multi-center, open-label, uncontrolled study to be conducted in the US. Duration of the study treatment period is up to 3 years.
Methodology	Monitoring of occurrence of pregnancies and evaluating the menstrual blood loss in the HMB subgroup

Type of control	Uncontrolled study
Number of subjects	Approximately 360 subject to enter the treatment period
Primary variable	Occurrence of pregnancies
Time point/frame of measurement for primary variable(s)	Treatment period of up to 3 years (total time of Mirena use up to 8 years).
Plan for statistical analysis	Analysis of primary variable: Primary Analysis: The Pearl index (PI) will be calculated as the number of pregnancies within years 6-8 of Mirena use per 100 women years, and the corresponding 2-sided 95% confidence interval will be provided. Secondary Analysis: The cumulative failure rate, i.e., the probability of getting pregnant will be calculated using the Kaplan Meier method in addition to the calculation of PIs.

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ADR	Adverse drug reaction
AE	Adverse event
AIDS	Acquired immune deficiency syndrome
ALT	Alanine aminotransferase
ASCUS	Atypical squamous cells of undetermined significance
AST	Aspartate aminotransferase
BL	Baseline
CI	Confidence interval
CRA	Clinical research associate
CRF	Case report form
CRO	Contract research organization
CSR	Clinical Study Report
CV	Coefficient of variation
DNA	Deoxyribonucleic acid
eCRF	Electronic case report form
e.g.	Exempli gratia (for example)
EMA	European Medicines Agency
EOS	End of study
EOT	End of treatment
FAS	Full analysis set
FDA	Food and Drug Administration
FPFV	First patient first visit
FSH	Follicle-stimulating hormone
GCL	Global Clinical Leader
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
HbA1c	Glycosylated hemoglobin
hCG	Human chorionic gonadotropin
HDL	High density lipoprotein
HIV	Human immunodeficiency virus
HMB	Heavy menstrual bleeding
HPV	Human papilloma virus
IB	Investigator's Brochure
ICF	Informed consent form
ICH	International Council on Harmonization
i.e.	Id est (that is)
IEC	Independent Ethics Committee
IME	Important Medical Event
IRB	Institutional Review Board
IUD	Intrauterine device
IUS	Intrauterine system
LC-MS	Liquid chromatography-mass spectrometry
LCS	Levonorgestrel contraceptive intrauterine system
LDL	Low density lipoprotein
LNG	Levonorgestrel
LPLV	Last patient last visit
mIU	milliInternational Unit
MBL	Menstrual blood loss
MCH	Mean corpuscular hemoglobin
MCV	Mean corpuscular volume
MedDRA	Medical Dictionary for Regulatory Activities
MET	Mirena Extended Trial
mg	milligram

MI	Myocardial infarction
mL	milliliter
MRP	Medical Review Plan
MS	Mass spectrometry
NAAT	Nucleic acid amplification tests
NJ	New Jersey
PAS	Primary analysis set
PCR	Polymerase chain reaction
PI	Pearl Index
PID	Pelvic inflammatory disease
PK	Pharmacokinetics
popPK	Population pharmacokinetic
PRO	Patient-reported outcomes
PT	Preferred term
PTPT	Post-Treatment Pregnancy Tracking
QC	Quality control
SAE	Serious adverse event
SAF	Safety analysis set
SE	Standard error
SHBG	Sex hormone binding globulin
SID	Subject identification (number)
SOC	System organ class
SOP	Standard Operating Procedure
STD	Sexually transmitted disease
STIs	Sexually transmissible infections
SUSARs	Suspected, unexpected, serious adverse reactions
TVUS	Transvaginal ultrasound
US	United States of America
WHO	World Health Organization

3. Introduction

Background

Mirena, a levonorgestrel-releasing intrauterine system (LNG IUS; initial in vitro release rate 20 µg LNG / day), has been proven a safe and reliable method of contraception over the 5 years of labeled use. It has been on the market since mid-1990s in most European countries and since 2001 in the United States (US).

This section was changed in Amendment 1, see Section 15.1.1.20.

Three contraceptive efficacy studies on extended use beyond the indicated 5 years up to 7 years (1, 2, 3) have been published. In a comparative study the effectiveness of the contraceptive implant and the 52-mg hormonal intrauterine device in women using the method for 2 years beyond the approved duration was evaluated (1). Among 496 LNG IUS users, 696.9 woman-years of follow-up have been completed. Two pregnancies have been reported. The failure rate in the sixth year of use of the LNG IUS is calculated as 0.25 (95% CI, 0.04-1.42) per 100 woman-years; failure rate during the seventh year is 0.43 (95% CI 0.08-2.39) per 100 woman-years. In the recently published study by Rowe et al 2016 (2), the overall pregnancy rate of the TCu380A was significantly higher than that of the LNG IUD: at the end of the seventh year the cumulative rate was 2.45 (standard error [SE] 0.44) per 100 for the TCu380A and 0.53 (SE 0.21) per 100 for the LNG IUD. In the earlier study (3), no pregnancies occurred to users of either device in years 6 and 7. Cumulative pregnancy rates were 1.1 per 100 at seven years for the LNG IUS and 1.4 per 100 for the copper-releasing IUDs. Hidalgo et al (2009) (4) evaluated the serum levonorgestrel levels and endometrial thickness during extended use of the levonorgestrel-releasing intrauterine system up to 8 1/2 years after insertion. During extended use of the LNG IUS, serum LNG levels were nearly half of those found in the first 2 months of use. Despite the very thin endometrium, menstrual bleeding was reinstated in many cases. The incidence of amenorrhea decreased from 41.8% at 84 months to 31.5% at 102 months of use (4).

The in vivo LNG release rate at the end of the 5 years of Mirena use is 10.1 µg/d which is higher than that for other LNG IUS, Jaydess (5.4 µg/d at 3 years) and LCS16 (7.4 µg/d at 5 years) (see Table 3–1), suggesting that the product would be efficacious in preventing pregnancy for a longer period of use.

This study will evaluate the contraceptive efficacy of Mirena during the extended use for up to 8 years. The stability of the effect on heavy menstrual bleeding during the extended use will be studied in a subgroup of women for whom the Mirena was prescribed for heavy menstrual bleeding (as a secondary indication to contraception).

Further details can be found in the latest available version of the investigator's brochure, which contains comprehensive information on the study drug.

Rationale of the study

Mirena has a high contraceptive efficacy resulting in a failure rate of approximately 0.2% at 1 year and a cumulative failure rate of approximately 0.7% at 5 years. In addition, Mirena has been shown to reduce menstrual blood loss by more than 90% after 1 year and to consequently increase blood hemoglobin levels (5). Clinical practice has shown that Mirena often relieves dysmenorrhea and premenstrual symptoms.

Mirena is currently indicated for use up to 5 years. Bayer wishes to study the extended duration of use of Mirena up to 8-years in the indication contraception. Depending on the results, this may allow recommendation of a longer interval between the IUS placements in women who may wish to continue use of Mirena for contraception beyond 5 years. The planned study will provide the basis for extension of Mirena use up to 8 years for contraception.

To support the extension of use over 8 years, a prediction of typical *in vivo* release rates for Mirena at 5, 6, 7, and 8 years after insertion of the IUD was performed using population pharmacokinetic (PK) methods. The prediction was based on residual content data from Report A15942 and a first-order release was assumed.

Table 3–1: Prediction of in vivo release rates based on residual content data from Report A15942

Time point after insertion	Mirena Residual LNG (mg)	Mirena Residual LNG (%)	Mirena *in vivo* release rate [µg/d]	Jaydess/Skyla *in vivo* release rate [µg/d]	LCS16 *in vivo* release rate [µg/d]
3 years	--	--	13.7	5.4	8.0
5 years	24.2	46.5%	10.1	--	7.4
6 years	20.7	39.9%	8.6	--	--
7 years	17.8	34.2%	7.4	--	--
8 years	15.3	29.3%	6.4	--	--

Table 3–1 shows the residual LNG content in the device after 5, 6, 7, and 8 years of use as amount in mg and in % of initial content (52 mg). Even after 8 years, about 30% of the initial content is still in the LNG IUS. The typical in vivo release rates for Mirena decline from about 10 µg/d to 6.4 µg/d after 8 years of use. Compared to Jaydess/Skyla, which is the LNG IUS with the lowest release rate on the market, the anticipated in vivo release rate for Mirena is still higher.

In support of the extended use of Mirena beyond 5 years, serum LNG concentrations (5 years and beyond, from Mirena in comparison with LCS16 and Jaydess/Skyla) are presented in Table 3–2 below:

Table 3–2: Comparison of average LNG serum concentrations (% CV) data of Jaydess/Skyla, LCS16 and Mirena

Time	Jaydess/Skyla (ng/L)	LCS16 (ng/L)	Mirena (ng/L)
3 years	68.5 (33.0%)[a]	85.2 (63.9%)[a]	165 (40.5%)[a]
5 years	-	64.0 (23.0%)[e]	150 (35.6%)[b]
6.5 years	-	-	76.3 (31.8%)[c]
8 years	-	-	117 (50.4%)[d]

Abbreviations: CV=coefficient of variation; LNG=levonorgestrel
a A46796 CSR (6)
b B078 CSR (7)
c B073 CSR (8)
d Seeber B, et al. 2012 (13)
e PH-37274 CSR (9)

The above data indicate that serum concentrations of LNG after 8 years of Mirena use are in a similar range compared to Jaydess/Skyla after 3 years of use as can be expected based on the similar in vivo release rates.

The simulated in vivo release rates for Mirena support the extended use up to 8 years.

Benefit-risk assessment

Benefit /risk balance for Mirena in Contraception:

Mirena has a very high contraceptive efficacy which is less dependent on user-compliance and compares favorably to other contraceptive methods including barrier methods, combined oral contraceptive, progestin-only pill, injectables, and copper IUDs (eg. ParaGard). Its efficacy is not influenced by hepatic enzyme-inducing drugs (in contrast to other hormonal methods). Further non-contraceptive benefits include decreased menstrual blood loss and alleviation of dysmenorrhea. Some studies have also suggested that Mirena may have beneficial effects on pelvic pain related to endometriosis or adenomyosis. Due to its mainly local mechanism of action and the fact that it does not contain estrogens, Mirena is suitable for many women in whom combined contraceptive methods are contraindicated or not desirable. Mirena can be inserted immediately after a first trimester abortion, with immediate effect of contraceptive efficacy. Mirena does not interfere with lactation.

The majority of Mirena users experience bleeding changes. Other "very common" adverse drug reactions (ADRs) in clinical trials include headache and abdominal/pelvic pain. Ovarian cysts are observed under Mirena use but are in the vast majority, transient and asymptomatic. Hormonal side effects of levonorgestrel are less frequently observed.

Identified safety risks are device related complications (such as expulsions), and side effects caused by levonorgestrel. Important safety risks/serious events are rare (pelvic inflammatory disease [PID], uterine perforation) and can be managed with adequate medical or surgical treatment. Clinical trials and observational studies have established that the risk of PID associated with insertion of intrauterine contraceptives is confined to the first weeks after insertion. A large European active surveillance study (EURAS-IUD) (10) showed that the

risk of uterine perforation is increased in women who are breastfeeding at time of insertion, or have given birth up to 36 weeks before insertion. However, the need for reliable contraception is high in this population, but contraceptive options in this population are restricted to methods not interfering with lactation.

Although the absolute rate of ectopic pregnancies with Mirena is lower than in subjects without any contraceptive method, the relative risk of ectopic pregnancy in women becoming pregnant while using Mirena is increased.

Intrauterine pregnancy, when occurring during use of Mirena, is associated with a higher risk for spontaneous abortion and premature delivery. The more common risks of bleeding changes, ovarian cysts and expulsions are non-serious.

Extension of Mirena use for contraception to 8 years

Extended duration of use of Mirena up to 8 years offers a benefit for those women who want to continue the use of Mirena beyond 5 years for contraception by extending the period in between the two consecutive LNG IUS and thus prolonging the time interval between IUS placements. By prolonging the time interval between IUS placements, the risk of IUS-insertion related complications is further reduced by reducing the number of IUS placements that will be necessary in women who choose to continue this method of contraception during a longer period of their fertile years. Reducing the number of times that a woman will have to expect the discomfort and the cost associated with the insertion of an intrauterine contraceptive may ultimately lead to increased use of a highly effective method of contraception.

Contraceptive efficacy during extended duration of use of Mirena during years 6, 7 and 8 is expected to be high, as the lower release rate of other LNG IUS products (Skyla and LCS16) have been proven to provide high efficacy with a Pearl Index of less than 0.5 up to 3 years (11) and 5 years (9). Risks associated with contraceptive failure (i.e. risk of ectopic pregnancy, and risk to a pregnancy with Mirena in situ) are not expected to change during years 6, 7 and 8 with continued high contraceptive efficacy, which will be demonstrated in the proposed clinical study.

The bleeding profile during the extended use of the same device is expected to remain favorable and similar to that observed during the use up to 5 years. The incidence of infrequent bleeding or absence of bleeding increase with time in users of LNG IUS, while the incidence of prolonged and frequent bleeding decreases. Absence of bleeding is associated with high overall satisfaction and continuation rates in women using a second consecutive Mirena (12).

The study will also analyze the removal procedure after 8 years of use to confirm the usability of the product for the extended duration of use. No new risks are anticipated.

In summary, a positive benefit risk balance is anticipated during the extended use of Mirena for contraception up to 8 years.

4. Study objectives

Primary objective of the study is to assess the contraceptive efficacy of Mirena beyond 5 years up to 8 years of use.

Secondary objectives for the study are the assessment of menstrual blood loss (in women that had Mirena inserted for the indication heavy menstrual bleeding [HMB]) and safety.

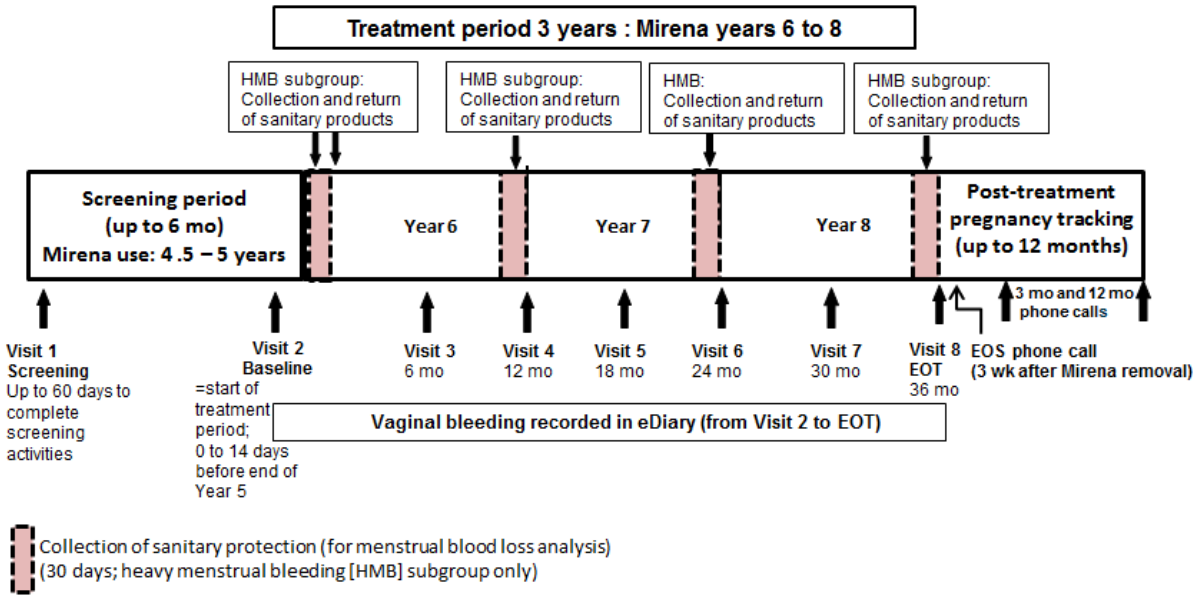
Further objectives are the population pharmacokinetic evaluation of LNG plasma concentration data and evaluation of user satisfaction.

5. Study design

Design overview

This is a multi-center, uncontrolled, single group study to be conducted in the US only. Study design is presented below in Figure 5—1.

Figure 5—1 Overview of the study design



The target for the total number of women to be included in the extended treatment period is 360 women (200 women to complete study treatment). To evaluate the effect of extended Mirena use on HMB, it is targeted that 10% of the women to be treated (i.e. 36 women out of 360) should have Mirena prescribed for the treatment of HMB in addition to contraception. Please note, subjects who have Mirena prescribed for contraception and heavy menstrual bleeding will have to consent to the HMB subgroup procedures.

The study will consist of a screening, treatment, and a follow-up period. Screening can be started when the subject has had the Mirena in place for 4 years and 6 months. Screening activities should be completed within 60 days after signed informed consent to allow enough time for the evaluation of the subjects' eligibility to the study. Baseline visit (Visit 2) will be scheduled to take place 0 to 14 days before the end of Year 5 of Mirena use; and this is the start of the treatment period. Treatment period is defined as the 3-year period following the Baseline visit, i.e. years 6, 7 and 8 of extended use of Mirena.

This section was changed in Amendment 1, see Section 15.1.1.1. An analysis of the efficacy and safety data will be conducted after all subjects have either completed 6 years of treatment (i.e. completed 1 year in the study), or prematurely terminated their study participation before this time point. Another analysis of the efficacy and safety data will be conducted after all subjects have either completed 7 years of treatment (i.e. completed 2 years in the study), or prematurely terminated their study participation before this time point.

Final analysis will be done after all subjects have either completed 8 years of treatment or prematurely terminated their study participation.

All subjects will be contacted 3 weeks after the EOT to collect information on any pregnancy detected shortly after the removal of Mirena. Follow-up period for the tracking of post-treatment pregnancies will be 3 months after the end of the treatment for subjects who prematurely discontinued study treatment. They will be contacted unless the reason for discontinuation is "pregnancy", "death", or "withdrawal by subject" where the subject has withdrawn main consent during study conduct and wishes to stop future contact with the site. For subjects that had withdrawn consent during study, but consented to post study participation follow-up, post treatment pregnancy tracking information is expected.

Follow-up period for the tracking of post-treatment pregnancies will be up to 12 months for subjects who discontinue Mirena use because of a wish for pregnancy (i.e. collection of return-to-fertility data). Subjects who discontinue treatment because of a wish for pregnancy will receive a second telephone call at 12 months after removal of the Mirena if they still wished for a pregnancy at the 3-month contact and had not reported a pregnancy at the time of the 3-month follow-up call.

Levels of LNG (plasma) and sex hormone binding globulin (SHBG) (serum) will be monitored by means of sparse blood sampling, and will be evaluated using a population PK approach. In addition, serum LNG and SHBG levels will also be determined at the Mirena removal in all subjects discontinuing the study prematurely. Similarly, residual LNG content will be determined after removal at the end of the study for all subjects who had entered the treatment period whether they completed the study or discontinued prematurely. The concentration values for LNG and SHBG and residual LNG content data will be entered into the database at pre-planned database opening. The results on population pharmacokinetics will be reported separately.

Primary variable

Primary efficacy variable is the occurrence of pregnancy.

Justification of the design

The efficacy and safety of Mirena for contraception and HMB has been proven in a large clinical development program for up to 5 years, while no company sponsored study data is currently available for use of Mirena beyond 5 years. New clinical data is therefore needed. The planned study will assess the contraceptive efficacy of Mirena during extended use beyond 5 years up to 8 years. In addition, approximately 10% of the total number of women in the study will have had Mirena prescribed for contraception and heavy menstrual bleeding; these subjects will form the HMB subgroup to show that the efficacy in terms of menstrual blood loss is maintained during extended use. This study design allows access for extended use of Mirena in women who have already been using Mirena close to the end of the currently approved maximum period of use and therefore an option for longer interval between the IUS placements in those women, who wish to continue use of Mirena for contraception or contraception and heavy menstrual bleeding (HMB) beyond 5 years.

End of study

The end of the study as a whole will be reached as soon as the last visit of the last subject (i.e. end of study phone call at 3 weeks after Mirena removal) has been reached in all centers.

Primary completion

The primary completion event for this study is the last patient last visit (LPLV).

The primary completion date for this study according to the FDA Amendment Act is specified in a separate document (not part of this study protocol).

6. Study population

This section was changed in Amendment 1, see Sections 15.1.1.2, 15.1.1.3, and 15.1.1.12.

The study will include fertile age women (18 to 35 years at the time of the screening visit) currently using a Mirena for contraception or for contraception and heavy menstrual bleeding and who have had the Mirena in situ for at least 4 years and 6 months but no longer than 5 years and are willing to continue its use for contraception or contraception and heavy menstrual bleeding for up to 8 years in total. About 90% of the women included will be 18 to 32 (inclusive) years of age at screening (visit 1)[1]. In addition, the aim is that approximately 10% of the total number of women in the study will have had Mirena prescribed for contraception and heavy menstrual bleeding; these subjects will form the HMB subgroup. Subjects who have Mirena prescribed for contraception and heavy menstrual bleeding will have to consent to the HMB subgroup procedures. The subjects must have a continuing need for contraception during the entire duration of the study (i.e. they are sexually active and at risk of pregnancy during the study treatment period of 3 years, i.e. up to a total of 8 years

[1] Screening of women who are 34 or 35 years old will be closed, once 10 women in this age group have completed the baseline visit, for details see Section 10.4.

with the current Mirena). Women who have contraindications to use Mirena according to the current US label will be excluded from participation in the study.

Women in need of contraception meeting all inclusion and presenting none of the exclusion criteria will be eligible for enrollment to the treatment phase in the study. Inclusion and exclusion criteria are checked at the screening visit. A re-check on eligibility is to be done at baseline visit.

6.1 Inclusion criteria

1. Signed and dated informed consent
2. Women, 18 to 35 years of age at the time of screening (visit 1) who are currently using Mirena for contraception or for contraception and heavy menstrual bleeding. The duration of use of the current Mirena has to be at least 4 years 6 months at the start of screening phase but not more than 5 years at visit 2 and the woman is willing to continue with its use and has a continuing need for contraception.
3. Normal or clinically insignificant cervical smear not requiring further follow up (a cervical smear has to be taken at screening visit or a normal result has to be documented within the previous 6 months). Human papilloma virus (HPV) testing in subjects with atypical squamous cells of undetermined significance (ASCUS) can be used as an adjunctive test. Subjects with ASCUS can be included provided they are negative for high-risk HPV strains.

6.2 Exclusion criteria

This section was changed in Amendment 1, see Sections 15.1.1.3 and 15.1.1.12.

1. Menopausal symptoms with FSH >30 mIU/ml
2. Pregnancy or suspicion of pregnancy
3. Uterine bleeding of unknown etiology
4. Untreated acute cervicitis or vaginitis or other lower genital tract infections (until successfully treated)
5. Increased susceptibility to pelvic infection
6. Acute pelvic inflammatory disease (PID) or a history of PID unless successfully treated and which, in the investigator's opinion, has not negatively affected subject's fertility
7. Congenital or acquired uterine anomaly if it distorts the uterine cavity
8. Known or suspected breast cancer or other progestin-sensitive cancer
9. History of, diagnosed or suspected genital or other malignancy (excluding treated squamous cell carcinoma of the skin), and untreated cervical dysplasia
10. Known or suspected uterine or cervical neoplasia
11. Any active acute liver disease or liver tumor (benign or malignant)
12. Clinically significant endometrial polyp(s), which, in the opinion of the investigator, will interfere with the assessment of the bleeding profile during the study.

13. Clinically significant ovarian cyst(s).
14. Concomitant use of other sex-hormone containing preparations
15. Hypersensitivity to any component of Mirena
16. Any diseases or conditions that can compromise the function of the body systems and could result in altered absorption, excessive accumulation, impaired metabolism, or altered excretion of the study medication
17. Any diseases or conditions that might interfere with the conduct of the study or the interpretation of the results
18. Abuse of alcohol, drugs, or medicine (e.g., laxatives)
19. Inability to cooperate with the study procedures for any reason, including the following examples: language comprehension, psychiatric illness, inability to get to the study site
20. Known or suspected HIV infection or high risk for STD. Conditions associated with increased susceptibility to infection with microorganisms, including such conditions as leukemia, human immunodeficiency virus (HIV)-positive status, acquired immune deficiency syndrome (AIDS).
21. Laboratory values outside inclusion range before baseline and considered clinically relevant (see Section 9.6.3.7).
22. Simultaneous participation in another clinical study with investigational medicinal product(s). Participation in another clinical trial prior to study entry that might have an impact on the study objectives, at the discretion of the investigator.
23. Close affiliation with the investigational site; e.g. a close relative of the investigator, dependent person (e.g. employee or student of investigational site, or sponsor's staff)
24. Previous enrollment to the study (i.e. re-screening allowed only as described in section 6.4.1)

6.3 Justification of selection criteria

The entry criteria defined for the study ensure selection of fertile women who are willing to continue with Mirena as their method of contraception. Entry criteria are chosen to ensure that subjects with specific risks related to the use of the study drug and/or subjects with conditions which may have an effect on the study endpoints are excluded.

6.4 Withdrawal of subjects from study

6.4.1 Withdrawal

Withdrawal criteria

This section was changed in Amendment 1, see Section 15.1.1.4 and 15.1.1.13.

Subjects *must* be withdrawn from the study if any of the following occurs:

- At their own request. At any time during the study and without giving reasons, a subject may decline to participate further. The subject will not suffer any disadvantage as a result.
- Complete or partial expulsion of the Mirena
- Removal of Mirena outside the study procedures
- Pregnancy
- Partial or total perforation of the uterus or cervix by Mirena
- Acute pelvic inflammatory disease (PID) not responding to treatment
- Genital malignancy (e.g., uterine or cervical malignancy)
- Severe arterial disease such as stroke or myocardial infarction (MI)
- Liver tumor (benign or malignant)
- Allergic reaction to the study medication or any of its components
- If, in the investigator's opinion, continuation of the study would be harmful to the subject's well-being
- Should the subject, during the course of the study, develop conditions which would have prevented her entry into the study according to the exclusion criteria, she must be withdrawn immediately if safety is concerned. In other cases, the investigator will decide if there is a conflict with study objectives.
- Participation in any other clinical study during the duration of this study

Subjects *may* be withdrawn from the study if any of the following occurs:

- Coagulopathy or use of anticoagulant
- Migraine, focal migraine with asymmetrical visual loss or other symptoms indicating transient cerebral ischemia
- Exceptionally severe headache
- Marked increase of blood pressure
- Jaundice
- Non-attendance of visits despite the efforts to reach the subject (i.e. if a subject does not attend consecutive visits without a major reason).

    - Every effort must be made to have the subject attend these visits in-person. However, once all attempts have been exhausted to have the subject come to the study site, if the subject is unable to do so during the allotted timeframe, the visit may be documented via phone. In these instances, the site should determine the most appropriate means for excluding that a pregnancy has occurred (e.g. home pregnancy test kit, menstrual history, etc). All methods and results regarding determination of pregnancy must be documented.
- Serious adverse event, adverse event, laboratory abnormality of considerable clinical concern or considerable worsening of the subject's clinical symptoms
- At the specific request of the sponsor and in liaison with the investigator (e.g. obvious non-compliance, safety concerns).
- Return of heavy menstrual bleeding, if it affects the subject's well-being, based on the investigator's clinical judgment

The reasons for any withdrawal are to be fully documented on the eCRF.

End of treatment visit (Visit 8) and the end of study phone call (3 weeks after the Mirena removal) must be performed also for all subjects discontinuing the study prematurely.

Depending on the time point of withdrawal, a withdrawn subject is referred to as either "screening failure" or "dropout" as specified below:

Screening failure

A subject who, for any reason (e.g. failure to satisfy the entry criteria), terminates the study before the time point used for the definition of "dropout" (i.e. before completion of the baseline visit, Visit 2) is regarded a "screening failure".

Re-starting the defined set of screening procedures to enable the "screening failure" subject's participation at a later time point is not allowed – with the following exceptions:

- Initial screening occurred too early, i.e. before 4 years and 6 months of the Mirena use
- The in- / exclusion criteria preventing the subject's initial attempt to participate have been changed (via protocol amendment).

In any case, the investigator has to ensure that the repeated screening procedures do not expose the subject to an unjustifiable health risk. Also, for re-screening, the subject has to re-sign the informed consent form, even if it was not changed after the subject's previous screening.

Dropout

A subject who discontinues study participation prematurely for any reason is defined as a "dropout" if the subject has already been deemed eligible to participate and completed the baseline visit (visit 2).

General procedures

In all cases, the reason for withdrawal must be recorded in the eCRF and in the subject's medical records.

The subject may object to the generation and processing of post-withdrawal data as specified in Section 13.4.

Any subject removed from the trial will remain under medical supervision until discharge or transfer is medically acceptable.

Details for the premature termination of the study as a whole (or components thereof) are provided in Section 12.

6.4.2 Replacement

Subjects who have completed the baseline visit (visit 2) and thereafter terminate their study participation prematurely will not be replaced.

6.5 Subject identification

The subject identification (SID) number is a 9-digit number consisting of:

Digits 1 to 5 = Unique center number

Digits 6 to 9 = Current subject number within the center

Once allocated, the SID number will identify the subject throughout the study.

If subject is re-screened, she will receive a new SID.

7. Treatments

7.1 Treatments to be administered

No study drug (Mirena) will be provided by the sponsor. Subjects enter this study treatment period wearing a Mirena that was inserted 5 years earlier and will continue its use for an additional 3 years, i.e. up to a total of 8 years. Subjects are required to provide documentation about the prescription for the Mirena (including indication) and the date of insertion.

Test drug is Mirena, an LNG intrauterine delivery system (IUS) with an initial in vitro release rate of 20 µg LNG per day, used continuously. The total LNG content in Mirena is 52 mg.

7.2 Identity of study treatment

See Section 7.1.

7.3 Treatment assignment

Not applicable, this is a single group study. A subject enters the study with a Mirena in the uterus.

7.4 Dosage and administration

The initial in vitro release rate is 20 µg LNG per day. The total LNG content in Mirena is 52 mg. Mirena has been inserted into the uterine cavity before the study, and will remain in place for up to a total of 8 years.

7.4.1 Removal of Mirena

Timing of removal

- Mirena should not remain in the uterus after 8 years.
- If pregnancy is not desired, the removal should be carried out during menstruation, provided the woman is still experiencing regular menses. If removal will occur at other times during the cycle, start a new contraceptive method a week prior to removal. If removal occurs at other times during the cycle and the woman has had intercourse in the week prior to removal, she is at risk of pregnancy. See also section 8.2.

7.5 Blinding

Not applicable

7.6 Drug logistics and accountability

Return of the study drug must be properly documented according to the sponsor's agreed and specified procedures. Written instructions will be made available to all affected parties.

Return of the Mirenas to the sponsor's representative

If a subject discontinues her study participation prematurely or completes the 8 years of use, the Mirena should be removed by gently pulling the removal thread(s) with forceps.

After removal (or if the subject returns an expelled Mirena to the study site) the Mirena is to be rinsed in cold water, dried carefully with a clean paper towel and packaged in a plastic pouch provided by the sponsor; the pouch label needs to be completed.

The used Mirena should be stored according to the pouch label text, in the provided pouches in locked storage facilities until returned to sponsor's representative.

If performing drug accountability implies a potential risk of contamination, a safety process/ guidance for handling returned drug will be provided.

In the event of Product Technical Complaint (e.g. technical difficulties with the IUS during removal, pregnancy, expulsion), the respective forms need to be completed and returned with the Mirena in question to sponsor´s representative for further investigation according to sponsor´s instructions.

7.7 Treatment compliance

Please refer to section 9.6.3.8.

8. Non-study therapy

8.1 Concomitant therapy

For the use of concomitant medications please refer to Section 6.2 (Exclusion criterion #14).

All medications taken during the study (i.e. starting with the date of informed consent) will be recorded in the eCRF using the trade name, indication, dose, unit, frequency, route of administration and dates of intake (i.e. start and stop dates).

8.2 Post-study therapy

The study subject should be informed that there will be a loss of contraceptive protection after the end of the study treatment, i.e. after removal of the Mirena.

The investigator will counsel the subject about the contraceptive options available after the study treatment (at Visit 7, or before end of the study).

If pregnancy is not desired and if a woman wishes to continue using Mirena, a new system can be inserted immediately after removal any time during the cycle.

If a subject with regular cycles wants to start a different birth control method, time removal and initiation of new method to ensure continuous contraception. Either remove Mirena during the first 7 days of the menstrual cycle and start the new method immediately thereafter or consider starting the new method at least 7 days prior to removing Mirena if removal is to occur at other times during the cycle. If removal occurs at other times during the cycle and the woman has had intercourse in the week prior to removal, she is at risk of pregnancy.

If a subject with irregular cycles or amenorrhea wants to start a different birth control method, consider starting the new method at least 7 days before removal.

Post-study birth control counseling will be done according to standard of practice, without the sponsor's involvement.

9. Procedures and variables

9.1 Tabular schedule of evaluations

This section was changed in Amendment 1, see Sections 15.1.1.1, 15.1.1.16, 15.1.1.24 and 15.1.1.25.

Table 9–1 presents the schedule of activities and evaluations for the study. The additional activities for the subjects in the HMB subgroup are displayed in Table 9–2.

Table 9–1 Schedule of activities and evaluations – *amended*

Period	**Screening (0 to 6 mo)**			**Treatment Period (3 years; Mirena years 6 thru 8)**						**Pregnancy Follow-up (up to 12 mo)**		
Visit	**Prescreening contact (optional)**	**Screening**	**Baseline**						**EOT[a]**	**EOS All subjects**	**3-mo contact [b]**	**12-mo contact [c]**
Visit number	☎/✉	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	☎	☎	☎
Timing		**within 60 days**	**Day 1**	**6 mo ±14 d**	**12 mo ±14 d**	**18 mo ±14 d**	**24 mo ±14 d**	**30 mo ±14 d**	**36 mo -14 d**	**3 wks after EOT -3 d**	**3 mo after EOT -7 d/+14 d**	**12 mo after EOT +7 d**
Duration of Mirena use		**4 y 6 mo to 5 years**	**5 years[d]**		**6 years**		**7 years**		**8 years**			
Informative discussion about the study/ Distribution of subject information	X	X										
Informed consent		X										
Indication for Mirena and date of insertion		X										
In-/exclusion criteria		X	X									
Demography		X										
Age at baseline			X									
Substance use - Tobacco		X										
Alcohol consumption		X										
Reproductive and menstrual history		X										
Medical history		X										
Physical examination		X			X		X		X			
Vital signs, body weight		X+height			X		X		X			
Gynecological exam. incl. breast palpation		X			X		X		X			
Checking of Mirena threads		X	X	X	X	X	X	X	X			
Cervical smear [e]		X							X			
Chlamydia test [f]		X										

Table 9–1 Schedule of activities and evaluations – *amended*

Period	**Screening (0 to 6 mo)**			**Treatment Period (3 years; Mirena years 6 thru 8)**						**Pregnancy Follow-up (up to 12 mo)**		
Visit	**Prescreening contact (optional)**	**Screening**	**Baseline**						**EOT[a]**	**EOS All subjects**	**3-mo contact [b]**	**12-mo contact [c]**
Visit number	☎/✉	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	☎	☎	☎
Timing		**within 60 days**	**Day 1**	**6 mo ±14 d**	**12 mo ±14 d**	**18 mo ±14 d**	**24 mo ±14 d**	**30 mo ±14 d**	**36 mo -14 d**	**3 wks after EOT -3 d**	**3 mo after EOT -7 d/+14 d**	**12 mo after EOT +7 d**
Duration of Mirena use		**4 y 6 mo to 5 years**	**5 years[d]**		**6 years**		**7 years**		**8 years**			
Urine pregnancy test [g]		X	X	X	X	X	X	X	X	X [g]		
Safety laboratory and urinalysis		X			X		X		X			
FSH		X										
Blood sample for PK [h]			X	X [i]	X [i]	X [i]	X [i]		X			
Concomitant medications		X	X	X	X	X	X	X	X			
Adverse events		X	X	X	X	X	X	X	X			
Continuing need for contraception				X	X	X	X	X	X			
Dispense home pregnancy test kits			X	X	X	X	X	X	X			
eDiary dispensed / collected			X						X			
Back-up contraception (if used; eDiary)			→	→	→	→	→	→	→			
Record uterine bleeding (daily, eDiary)			→	→	→	→	→	→	→			
Review of bleeding diary with subject				X	X	X	X	X	X			
Subject satisfaction with Mirena			X		X		X		X			
Mirena removal									X			
Mirena removal: ease and pain assessment									X			

Table 9–1 Schedule of activities and evaluations – *amended*

Period	**Screening (0 to 6 mo)**			**Treatment Period (3 years; Mirena years 6 thru 8)**						**Pregnancy Follow-up (up to 12 mo)**		
Visit	**Prescreening contact (optional)**	**Screening**	**Baseline**						**EOT[a]**	**EOS All subjects**	**3-mo contact [b]**	**12-mo contact [c]**
Visit number	☎/✉	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	☎	☎	☎
Timing		**within 60 days**	**Day 1**	**6 mo ±14 d**	**12 mo ±14 d**	**18 mo ±14 d**	**24 mo ±14 d**	**30 mo ±14 d**	**36 mo -14 d**	**3 wks after EOT -3 d**	**3 mo after EOT -7 d/+14 d**	**12 mo after EOT +7 d**
Duration of Mirena use		**4 y 6 mo to 5 years**	**5 years[d]**		**6 years**		**7 years**		**8 years**			
Documentation of pregnancy/return to fertility										X	X	X

Please see next page for footnotes

Footnote Explanations:

a An End-of-Treatment Visit must be performed also for all subjects who discontinue treatment. If a subject prematurely discontinues treatment, all efforts should be made to perform all the assessments scheduled for this EOT visit (Visit 8) including the EOS phone contact 3 weeks after the removal of Mirena before the subject is withdrawn from the study.

b For subjects who prematurely discontinued study treatment unless the reason for discontinuation is “pregnancy”, “death”, or “withdrawal by subject” where the subject has withdrawn main consent during study conduct and wishes to stop future contact with the site. Subjects that had withdrawn consent during study, but consented to post study participation follow-up will be contacted at this point. See also Section 9.4.1.

c Subjects that prematurely discontinued treatment due to ‘Wish for pregnancy’ will be contacted. If a subject was not pregnant at 3 month contact and no longer wished to become pregnant, a 12-month contact is not required. If a subject was “Lost to Follow-up” at 3 month contact, a 12-month contact is required. See also Section 9.4.1.

d The baseline visit (Visit 2) should take place 14 to 0 days before the end of Year 5 of Mirena use.

e A cervical smear should be taken at the Screening Visit or a documented normal result must have been obtained not more than 6 months before screening. Subjects with ASCUS can be included if they have an HPV DNA test that, according to the standards of the central or local laboratory, is negative for high-risk HPV strains. A single repeat test is permissible if the screening results are abnormal.

f If Chlamydia test is positive, also test for gonorrhea. A single repeat test is permissible if the screening results are positive

g In addition to the urine pregnancy tests performed by the site at each study visit, subjects will be given home urine pregnancy tests to be used whenever a pregnancy is suspected. Subjects must contact the study site immediately if a pregnancy test is positive. Home pregnancy test is to be done on the day of the 3-week contact.

h PK sampling: All subjects: one sample to be taken at baseline and at EOT (or if subject prematurely discontinues prior to removal) per subject; and two randomized samples to be taken at two of the visits 3 – 6.

i PK sampling for subjects randomized to this visit.

d=day, EOS=end of study, EOT=end of treatment, mo=month, PK=pharmacokinetics, wks=weeks, y=year

Subjects in the HMB subgroup (i.e. all women who had the Mirena inserted for contraception and heavy menstrual bleeding) will collect their used sanitary products (provided by sponsor) during 4 periods of 30 days as shown in Table 9–2. All used sanitary products have to be returned to the study site as instructed in Section 9.4.2 and displayed in Table 9–2.

For subjects who have the Mirena inserted for contraception only: if bleeding irregularities develop during prolonged treatment, appropriate diagnostic measures should be taken by the investigator to rule out endometrial pathology.

Table 9–2 Schedule of activities needed for the MBL evaluations – *amended*

HMB subgroup only – additional activities for baseline (BL) visit and treatment period. For all other activities and evaluations, see Table 9–1.

Period	**Screening**	**Treatment Period (Mirena years 6 thru 8)**										
Collection time		**30 days after baseline visit, Study Days 2 to 31 (inclusive)**			**Study Days 322 to 351 (inclusive) before Visit 4**			**Study Days 687 to 716 (inclusive) before Visit 6**			**Study Days 1052 to 1081 (inclusive) before EOT visit**	
Visit / visit number	**Baseline (BL) Visit 2**	**Return**	**Return**	**Visit 3**	**Return**	**Visit 4**	**Visit 5**	**Return**	**Visit 6**	**Visit 7**	**Return**	**EOT Visit 8**
Dispense alkaline hematin kit	X			X			X			X		
Collection of used sanitary products		→	→		→	→		→	→		→	→
Return of used sanitary products[a]		X	X		X	X		X	X		X	X

Study Day 1 = Day of the baseline visit (Visit 2)

a Used sanitary products should not be kept at home longer than 14 days. Return required only if sanitary products have been used in the time periods indicated.

9.2 Visit description

General information

Timing of the visits

If not stated otherwise, the measures listed in the following sections will be performed by or under the supervision of a study site investigator.

There will be 8 scheduled study visits: screening visit (Visit 1), baseline visit (Visit 2), 5 visits during the treatment phase (Visit 3 to 7) and the end-of-treatment visit (EOT, Visit 8). The end-of-study visit (EOS) is a phone contact at 3 weeks after the EOT (all subjects).

In addition, there will be up to 2 follow-up contacts for post-treatment pregnancy tracking. 3-month follow-up contact is for subjects who prematurely discontinued study treatment unless the reason for discontinuation is "pregnancy", "death", or "withdrawal by subject" where the subject has withdrawn main consent during study conduct and wishes to stop future contact with the site. For subjects that had withdrawn consent during study, but consented to post study participation follow-up, will be contacted. If subjects could not be contacted at 3 months, they will be considered "Lost to Follow-up" for post-study pregnancy tracking. 12-month contact is for subjects that prematurely discontinued treatment due to 'Wish for pregnancy'. If a subject was not pregnant at 3-month contact but subject no longer wished to become pregnant, a 12-month contact is not required. If subject was "Lost to Follow-up" at 3 months, a 12-month contact is required. For details, see Section 9.4.1.2.

The screening period can start when the subject has had the Mirena in place for 4 years and 6 months. Screening period is up to 6 months. Screening activities should be completed within 60 days after signing the informed consent. The baseline visit (Visit 2) should take place 14 to 0 days before the end of Year 5 of Mirena use.

The timing of the visits is based on the date of the baseline visit. Treatment period starts at the baseline visit (Visit 2, defined as Study Day 1).

The following visit windows are allowed:

- Visits 3 to 7 (during treatment) should be performed ±2 weeks of the scheduled day.
- Visit 8 (EOT) should be performed at the earliest 2 weeks before the scheduled day and not later.
- Follow-up contact (EOS) should take place 3 weeks after the EOT (-3 day window allowed.

Unscheduled visits

If deemed necessary for an individual subject, the investigator, at his/her discretion, may arrange visits in addition to the scheduled study visits. Possible reasons for unscheduled visits include suspicion of pregnancy and a safety concern.

Informed consent

Before any screening examination takes place, potentially eligible subjects will be given a full explanation about what the participation in the study would involve. This will be done both verbally and in writing by handing out the subject information sheet and informed consent

form by investigator or designee. Subjects will be given sufficient time to consider their participation in the study and to ask any questions about the study. Subjects willing to take part in the study will then be asked to sign and date the informed consent form (see Section 13.4).

Screening examinations will only be performed after the site staff has received the subject's signed and dated informed consent form.

9.2.1 Optional pre-screening contact

Before the screening visit (Visit 1), an optional pre-screening contact can be arranged and will typically occur via telephone or as a response to an advertisement. During this contact, the study candidate may be interviewed for suitability to participate in the study consistent with the entry criteria of the study. The pre-screening contact may be performed by the investigator, study nurse, or other member of the study staff specifically trained for this task.

After the pre-screening telephone discussion, the subject information form and the informed consent form may be sent to the subject for further information. Regardless of whether the subject information form is sent to the subject, the details of the study must be thoroughly discussed and reviewed with the subject at the screening visit (Visit 1) before obtaining the signed informed consent form.

9.2.2 Screening – Visit 1

At the Screening Visit (Visit 1), the following procedures and assessments will be done:

- Informative discussion about the study; distribution of subject information form.
  Note: This must occur at the Screening Visit even if the subject information form was sent to the subject following a pre-screening contact.
- Obtain signed and dated ICF (Section 13.4); allocate the unique SID number (Section 6.5)
- Record the prescribed indication for Mirena and the date of Mirena insertion (documentation required, see also Section 7.1)
- Check of inclusion/exclusion criteria (Sections 6.1 and 6.2)
- Interview for the following:
  - Demographics, alcohol consumption, and smoking habits (Section 9.3.1)
  - Medical history (Section 9.3.2)
  - Reproductive and menstrual history (Section 9.3.3)
  - Concomitant medications (Section 8.1)
  - AEs (Section 9.6.1. The recording period of AEs begins at the signing of the ICF)
- Perform urine pregnancy test (Section 9.6.3.4)
- Assess vital signs and weight (including **height**; Section 9.6.3.1)
- Perform general physical examination (Section 9.6.3.2)
- Perform gynecological examination (with **breast palpation**; Section 9.6.3.3)

- Perform pelvic examination to visualize Mirena removal threads (Section 9.6.3.8)
- Perform safety laboratory tests (including **FSH**) and urinalysis (Section 9.6.3.7)
- Test for *Chlamydia*; if positive, also test for gonorrhea (Section 9.6.3.6). A single repeat test is permissible if the screening results are positive.
- Obtain cervical smear (Section 9.6.3.5). A cervical smear should be taken at this visit or a documented normal result (using the Bethesda system or a corresponding system) has to have been obtained within 6 months before the Screening Visit (Visit 1). Subjects with ASCUS can be included if they have a HPV DNA test that, according to the standards of the local laboratory, is negative for high-risk HPV. A cervical smear may be repeated once if the screening result is abnormal.

9.2.3 Baseline – Visit 2

This section was changed in Amendment 1, see Section 15.1.1.25.

The following procedures and assessments will be done:

- Re-check inclusion/exclusion criteria (Sections 6.1 and 6.2)
- Age at baseline (Section 9.3.1)
- Perform pelvic examination to visualize Mirena removal threads (Section 9.6.3.8)
- Perform urine pregnancy test (Section 9.6.3.4)
- Blood sample for PK (**all subjects**) (Section 9.5.1)
- Subject satisfaction with Mirena (Section 9.7.4)
- Interview for the following:
    - Concomitant medications (Section 8.1)
    - AEs (Section 9.6.1)
- Dispense and explain the subject's daily eDiary device (Section 9.7.1), remind the subject to start the eDiary at the day of the visit (i.e. recording of uterine bleeding and back-up contraception)
- Dispense home pregnancy kits with instructions (Section 9.6.3.4)
- Dispense alkaline hematin kit with instructions for subjects in HMB group

9.2.4 6-month visit – Visit 3

The following procedures and assessments will be done:

- Perform pelvic examination to visualize Mirena removal threads (Section 9.6.3.8)
- Perform urine pregnancy test (Section 9.6.3.4)
- Blood sample for PK (Note: **subjects randomized to this visit**) (Section 9.5.1)
- Interview for the following:
    - Concomitant medications (Section 8.1)
    - AEs (Section 9.6.1)
    - Continuing need for contraception (Section 9.7.1)

- Dispense home pregnancy kits with instructions (Section 9.6.3.4)
- Review completed (monthly) eDiary, including information on uterine bleeding and back-up contraception.
- Dispense alkaline hematin kit with instructions for subjects in HMB group

9.2.5 12-month visit – Visit 4 (End of Year 6 of Mirena use)

This section was changed in Amendment 1, see Section 15.1.1.1.

The following procedures and assessments will be done:

- Assess vital signs and weight (Section 9.6.3.1)
- Perform general physical examination (Section 9.6.3.2)
- Perform gynecological examination (with **breast palpation**; Section 9.6.3.3)
- Perform pelvic examination to visualize Mirena removal threads (Section 9.6.3.8)
- Perform urine pregnancy test (Section 9.6.3.4)
- Perform safety laboratory test and urinalysis (Section 9.6.3.7)
- Blood sample for PK (Note: **subjects randomized to this visit**) (Section 9.5.1)
- Interview for the following:
    - Concomitant medications (Section 8.1)
    - AEs (Section 9.6.1)
    - Continuing need for contraception (Section 9.7.1)
- Dispense home pregnancy kits with instructions (Section 9.6.3.4)
- Review completed (monthly) eDiary, including information on uterine bleeding and back-up contraception.
- Subject satisfaction with Mirena (Section 9.7.4).

9.2.6 18-month visit – Visit 5

The following procedures and assessments will be done:

- Perform pelvic examination to visualize Mirena removal threads (Section 9.6.3.8)
- Perform urine pregnancy test (Section 9.6.3.4)
- Blood sample for PK (Note: **subjects randomized to this visit**) (Section 9.5.1)
- Interview for the following:
    - Concomitant medications (Section 8.1)
    - AEs (Section 9.6.1)
    - Continuing need for contraception (Section 9.7.1)
- Dispense home pregnancy kits with instructions (Section 9.6.3.4)
- Review completed (monthly) eDiary, including information on uterine bleeding and back-up contraception.
- Dispense alkaline hematin kit with instructions for subjects in HMB group

9.2.7 24 –month visit – Visit 6 (End of Year 7 of Mirena use)

The following procedures and assessments will be done:

- Assess vital signs and weight (Section 9.6.3.1)
- Perform general physical examination (Section 9.6.3.2)
- Perform gynecological examination (with **breast palpation**; Section 9.6.3.3)
- Perform pelvic examination to visualize Mirena removal threads (Section 9.6.3.8)
- Perform urine pregnancy test (Section 9.6.3.4)
- Perform safety laboratory test and urinalysis (Section 9.6.3.7)
- Blood sample for PK (Note: **subjects randomized to this visit**) (Section 9.5.1)
- Interview for the following:
    - Concomitant medications (Section 8.1)
    - AEs (Section 9.6.1)
    - Continuing need for contraception (Section 9.7.1)
- Dispense home pregnancy kits with instructions (Section 9.6.3.4)
- Review completed (monthly) eDiary, including information on uterine bleeding and back-up contraception
- Subject satisfaction with Mirena (Section 9.7.4).

9.2.8 30-month visit – Visit 7

This section was changed in Amendment 1, see Section 15.1.1.21.

The following procedures and assessments will be done:

- Perform pelvic examination to visualize Mirena removal threads (Section 9.6.3.8)
- Perform urine pregnancy test (Section 9.6.3.4)
- Interview for the following:
    - Concomitant medications (Section 8.1)
    - AEs (Section 9.6.1)
    - Continuing need for contraception (Section 9.7.1)
- Dispense home pregnancy kits with instructions (Section 9.6.3.4)
- Review completed (monthly) eDiary, including information on uterine bleeding and back-up contraception.
- Dispense alkaline hematin kit with instructions for subjects in HMB group.

Discuss the contraceptive options available after the study treatment with the subject (see Section 8.2).

9.2.9 36-month visit, EOT – Visit 8 (End of Year 8 of Mirena use)

This section was changed in Amendment 1, see Section 15.1.1.17.

The following procedures and assessments will be done:

- Assess vital signs and weight (Section 9.6.3.1)
- Perform general physical examination (Section 9.6.3.2)
- Perform gynecological examination (with **breast palpation**; Section 9.6.3.3)
- Perform pelvic examination to visualize Mirena removal threads (Section 9.6.3.8)
- Obtain cervical smear (Section 9.6.3.5)
- Perform urine pregnancy test (Section 9.6.3.4)
- Perform safety laboratory test and urinalysis (Section 9.6.3.7)
- Blood sample for PK (**all subjects**) (Section 9.5.1)
- Interview for the following:
    - Concomitant medications (Section 8.1)
    - AEs (Section 9.6.1)
    - Continuing need for contraception (Section 9.7.1)
- Dispense home pregnancy kits with instructions (Section 9.6.3.4)
- Review completed (monthly) eDiary, including information on uterine bleeding and back-up contraception.
- Collect eDiary device (Section 9.7.1)
- Subject satisfaction with Mirena (Section 9.7.4)
- Remove the Mirena (Section 9.7.3)
- Complete Mirena removal ease (investigator) and pain (subject) assessment

9.2.10 3-week follow-up call (EOS)

All subjects will be contacted 3 weeks after EOT (i.e. after Mirena removal) to collect information on any pregnancy detected shortly after the end of study treatment, see Section 9.4.1.

9.2.11 3-month follow-up contact for post-study pregnancies

This section was changed in Amendment 1, see Section 15.1.1.6.

Subjects who prematurely discontinued study treatment will be contacted by phone unless the reason for discontinuation is “pregnancy”, “death”, or “withdrawal by subject” where the subject has withdrawn main consent during study conduct and wishes to stop future contact with the site. For subjects that had withdrawn consent during study, but consented to post study participation follow-up, post treatment pregnancy tracking information is expected. At this time, subjects will be asked if they have been pregnant after the study (i.e. after the 3-week follow-up call). This contact is part of the Post-Treatment Pregnancy Tracking (PTPT) process, see Section 9.4.1.

9.2.12 12-month follow-up contact for return-to-fertility

This section was changed in Amendment 1, see Section 15.1.1.6.

Subjects that prematurely discontinued treatment due to 'Wish for pregnancy' will be contacted and asked about pregnancies that occurred within 12 months after end of treatment (EOT, i.e. removal of Mirena). If a subject was not pregnant at 3 month contact and no longer wished to become pregnant, a 12-month contact is not required. If subject was "Lost to Follow-up" at 3 months, a 12-month contact is required. This contact is part of the Post-Treatment Pregnancy Tracking (PTPT) process, see Section 9.4.1.

9.3 Population characteristics

9.3.1 Demographic

This section was changed in Amendment 1, see Section 15.1.1.25.

Demographic data [e.g. year of birth, age at the screening (Visit 1), age at baseline (Visit 2), race, ethnic group, educational level] and other population characteristics including tobacco use and alcohol consumption will be collected at time points presented in Table 9–1.

9.3.2 Medical history

Medical history findings (i.e. previous diagnoses, diseases or surgeries) meeting all criteria listed below will be collected as available to the investigator:

- Start before signing of the informed consent
- Considered relevant for the subject's study eligibility
- Any condition that is being stabilized by medication at the time of signing the informed consent form should also be documented in the eCRF. The medication being used should be recorded in the concomitant medication eCRF.

All new or worsened findings after signing the informed consent should be documented on the Adverse Event eCRF.

Detailed instructions on the differentiation between (i) medical history and (ii) adverse events can be found in Section 9.6.1.1.

9.3.3 Reproductive and menstrual history

The reproductive and menstrual history includes information on menarche, number of births and pregnancies, number of ectopic pregnancies, absence of menstrual/withdrawal bleeding, intracyclic bleeding and on the average length of the cycle.

9.3.4 Other baseline characteristics

9.3.4.1 Indication for current Mirena

The subject must provide written documentation from the prescribing physician on the indication for which the current Mirena was prescribed (contraception or contraception and heavy menstrual bleeding). The indication is recorded in the eCRF. In addition, subject must provide documentation of the date of Mirena insertion.

9.4 Efficacy

This section details the procedures for collecting data on efficacy variables. A concise listing of efficacy variables is given in Section 10.3.1.1. The complete list of variables to be analyzed for this study will be provided in the statistical analysis plan.

9.4.1 Occurrence of pregnancies

The occurrence of a pregnancy (yes/no) is the primary efficacy variable in this study.

The sponsor will closely monitor the occurrence of pregnancies (based on the expedited reporting of pregnancies by the investigators) throughout the study.

9.4.1.1 Pregnancies during the study

This section was changed in Amendment 1, see Section 15.1.1.6.

If a pregnancy is detected anytime during the study, the subject is to discontinue her participation in the study.

The investigator must report to the sponsor any pregnancy occurring in a study subject during her participation in this study including pregnancies detected at the contact 3 weeks after EOT. This report is to be submitted within the same timeframe as an SAE (i.e. no later than 24 hours of having gained knowledge of the event), although a pregnancy, per se, is not considered an AE/SAE.

The subject will be instructed to contact the study site immediately if a pregnancy is suspected or detected. In such a case, an unscheduled visit should be arranged for the subject as soon as possible and the investigator should confirm the pregnancy by a valid method (e.g. ultrasound, serum hCG test). If such confirmation cannot be achieved within **24 hours** of the subject contacting the study center, the investigator must still report the pregnancy to the sponsor and then follow-up with information once confirmation has been obtained.

A pregnancy will be reported on the forms provided. The investigator is required to document, as far as possible, the estimated date of conception, calculated due date, the reason for pregnancy (e.g., Mirena failure), location of the pregnancy, and, if applicable, the location of the Mirena and information regarding whether the Mirena was removed during the pregnancy. The investigator is required to provide any additional information (e.g. early termination) as soon as it becomes available.

All pregnancies occurring during the study (including those detected during the screening period) will be followed for the final outcome of the pregnancy for both the subject (mother) and fetus/child and documented on the forms provided. Any abnormal outcome of the mother or the child should also be reported as an SAE (e.g., spontaneous abortion, pre-term birth, elective abortion triggered by medical concern).

9.4.1.2 Pregnancies occurring after the end of study treatment

This section was changed in Amendment 1, see Sections 15.1.1.5 and 15.1.1.6.

All pregnancies detected up to 3 months after the removal of the Mirena must be reported to the sponsor; all subjects will be instructed to contact the investigator immediately if they

become pregnant less than 3 months after the removal of the Mirena. If the estimated date of conception is suspected to have occurred during study treatment (i.e. up to 7 days after EOT), further investigations will be conducted, and the pregnancy should be reported immediately and will be followed up according to the process described above for pregnancies during the study.

3-month follow-up contact: In addition, subjects who prematurely discontinued study treatment will be contacted unless the reason for discontinuation is "pregnancy", "death", or "withdrawal by subject" where the subject has withdrawn main consent during study conduct and wishes to stop future contact with the site. For subjects that had withdrawn consent during study, but consented to post study participation follow-up, post-treatment pregnancy tracking information is expected and they will be contacted by phone at 3 months after the removal of the Mirena. At this time, subjects will be asked if they have been pregnant after the study. If subjects could not be contacted at 3 months, they will be considered "Lost to Follow-up" for post-study pregnancy tracking.

12-month follow-up contact: Only subjects that prematurely discontinued treatment due to 'Wish for pregnancy' will be contacted and asked about pregnancies that occur within 1 year after end of treatment (EOT). If a subject was not pregnant at 3 month contact and no longer wishes to become pregnant, a 12-month contact is not required. If subject was "Lost to Follow-up" at 3 months, a 12-month contact is required.

PTPT information, i.e. data collected at the 3- and 12-month follow-up contacts, including information on all pregnancies identified, must be reported to the sponsor via electronic data collection tool (see Section 11.1). In addition, if the estimated date of conception is suspected to have occurred during study treatment, the pregnancy should be reported immediately according to the process described under section 9.4.1.1.

9.4.2 Assessment of menstrual blood loss (MBL) by alkaline hematin method

For the subjects in the HMB subgroup, the MBL will be assessed 4 times during the study. The 30-day assessment periods are scheduled as the first 30 days of the treatment period (starting at baseline visit, Visit 2) and for the 30 days before visits 4, 6 and 8. The subjects in this subgroup will be required to use the selected types of sanitary products (towels, tampons and panty liners) provided by the sponsor and to collect their used sanitary products during these 4 periods. Subjects will return the used products to the study site at two week intervals, and all used sanitary products will be sent to the central laboratory for analysis. Please see Table 9–2 for timing of the 4 periods and the required visits.

Details of the alkaline hematin method are given in the lab manual.

9.5 Pharmacokinetics / pharmacodynamics

9.5.1 Sample collection

Blood samples for the determination of LNG concentrations in plasma and sex hormone binding globulin (SHBG) concentrations in serum for population pharmacokinetic (popPK) analysis will be taken at several time points during the study according to the schedule presented in Table 9–1. A blood sample is taken from all subjects at baseline (visit 2) and at

the EOT (visit 8; **before** Mirena is removed). In addition, two blood samples per subjects will be taken during two of the treatment visits 3 – 6 as outlined in more detail below.

In case a subject prematurely discontinues the study, a blood sample will be taken in addition, even if the 2 randomized samples (visit 3 – 6) have already been taken at a previous visit. **This sample will always be taken before Mirena is removed.** (If Mirena has been completely expelled, no sample is needed.)

In order to achieve an approximately equal distribution of blood samples over the whole treatment period, the time points at which the samples are taken from each subject will be randomized. This means that the sampling time points for each subject will be allocated to two of the 4 treatment period visits (visits 3 – 6). Subjects will be allocated to one of these sampling time points with the same probability, i.e., with the probability 1:4. The allocation of subjects to sample time points for popPK will be done using a computer generated randomization list. The time points at which the samples are to be taken from an individual subject can be found on the randomization list provided to the study site.

The pharmacokinetic calculation will be based on the actual sampling time and dosing times. Deviations from the specified time points will be documented and taken into account when calculating the PK parameters.

Details to the collection, processing, storage and shipment of samples will be provided in a separate document (e.g. Sample Handling Sheets or Lab Manual).

9.5.2 Drug measurements

The bioanalytical analyses will be performed under the supervision of the function Drug Metabolism and Pharmacokinetics, Bayer AG.

Determination of LNG in plasma and SHBG in serum

The analyses of LNG concentrations in EDTA K_2 plasma will be performed using a validated LC-MS/MS method. The determination of SHBG concentrations in serum samples will be performed using a validated immunoassay. Quality control (QC) and calibration samples will be analyzed concurrently with study samples. The results of LNG and SHBG concentrations as well as the results of calibration samples and QC samples will be reported in the Bioanalytical Reports which will be included in the Clinical Study Report for this study.

Additionally, representative study samples may be used for further pharmacokinetic analyses, e.g. for a validation of a SHBG binding modeling compared to actual measurements.

9.5.3 Pharmacokinetic evaluation

Plasma LNG and SHBG concentration data collected during the study will be analyzed at the end of study by population PK analysis using nonlinear mixed effects models. Mixed effects models, or population type models, describe the relationship between e.g. dose, time and pharmacological observations such as plasma/serum drug concentrations. Both structural and random effects are involved in this relationship. An existing population PK model will be applied to the data and refined to characterize the PK of LNG over the entire treatment period (during years 6 to 8) using individual LNG serum (or plasma) concentrations, SHBG serum concentrations and residual content measurements of LNG in the IUS. Individual PK

parameters of total and unbound LNG and SHBG as well as *in vivo* release rates will be calculated. The details of the analysis will be described in a separate Modeling & Simulation (M&S) Analysis Plan and the results will be reported in a separate M&S Report.

9.5.4 Residual LNG content analysis

In order to evaluate the performance of Mirena during extended use, the residual content of LNG in used Mirena devices will be determined from all subjects at the end of treatment (i.e. from those who complete the 3 years in the study and from those who discontinue the study treatment prematurely). All used Mirena devices are to be sent to the sponsor's representative.

9.6 Safety

9.6.1 Adverse events

9.6.1.1 Definitions

Definition of adverse event (AE)

In a clinical study, an AE is any untoward medical occurrence (i.e. any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a patient or clinical investigation subject after providing written informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

A surgical procedure that was planned prior to the start of the study by any physician treating the subject should not be recorded as an AE (however, the condition for which the surgery is required may be reported in the medical history or may be an AE, (see below).

In the following differentiation between medical history and AEs, the term "condition" may include abnormal e.g. physical examination findings, symptoms, diseases and laboratory findings

- Conditions that started before signing of informed consent and for which no symptoms or treatment are present until signing of informed consent are recorded as medical history (e.g. seasonal allergy without acute complaints).
- Conditions that started before signing of informed consent and for which symptoms or treatment are present after signing of informed consent, at *unchanged intensity*, are recorded as medical history (e.g. allergic pollinosis).
- Conditions that started or deteriorated after signing of informed consent will be documented as adverse events. This includes intercurrent illnesses.

Definition of serious adverse event (SAE)

An SAE is classified as any untoward medical occurrence that, at any dose, meets any of the following criteria (a – f):

a. Results in death

b. Is life-threatening

   The term 'life-threatening' in the definition refers to an event in which the subject was at risk of death at the time of the event, it does not refer to an event which hypothetically might have caused death if it were more severe.

c. Requires inpatient hospitalization or prolongation of existing hospitalization

   A hospitalization or prolongation of hospitalization will not be regarded as an SAE if at least one of the following exceptions is met:

   - The admission results in a hospital stay of less than 12 hours
   - The admission is pre-planned
     (e.g. elective or scheduled surgery arranged prior to the start of the study; admission is part of the study procedures as described in Section 9.2)
   - The admission is not associated with an AE
     (e.g. social hospitalization for purposes of respite care).

   However, it should be noted that invasive treatment during any hospitalization may fulfill the criterion of 'medically important' and as such may be reportable as an SAE dependent on clinical judgment. In addition, where local regulatory authorities specifically require a more stringent definition, the local regulation takes precedence.

d. Results in persistent or significant disability / incapacity

   Disability means a substantial disruption of a person's ability to conduct normal life's functions.

e. Is a congenital anomaly / birth defect

f. Is another serious or important medical event as judged by the investigator

Important medical events and medical review

An AE may be considered serious because it may jeopardize the subject and may require intervention to prevent another serious condition. As guidance for determination of important medical events, the List of Important Medical Events (IME) developed and published by European Medicines Agency (EMA) at (http://eudravigilance.ema.europa.eu/human/textforIME.asp) will be used in this study. The list consists of terms that refer to or might be indicative of a serious disease state. Such reported events warrant special attention because of their possible association with a serious disease state and may lead to more decisive action than reports on other terms.

All non-serious AEs reported in this study will be reviewed against the most current IME list periodically. Events that are contained on the IME list will be specifically reviewed by the

Study Medical Expert, and if necessary, may be queried. If needed, the Investigator will be asked to review and confirm whether or not the event meets the criteria for seriousness, in his/her opinion. In addition, the events listed in Section 9.6.3 will be medically reviewed. Any non-serious event that, upon further review, is deemed to meet the seriousness criteria (see SAE criteria specified below) will be reported within 24 hours of the determination that it is considered serious.

Further details of the medical review to be conducted during the study are provided in a separate document, the Medical Review Plan (MRP), which is to be finalized and signed prior to the First Patient First Visit (FPFV).

9.6.1.2 Classifications for adverse event assessment

All AEs will be assessed and documented by the investigator according to the categories detailed below.

9.6.1.2.1 Seriousness

For each AE, the seriousness must be determined according to the criteria given in Section 9.6.1.1.

9.6.1.2.2 Intensity

The intensity of an AE is classified according to the following categories:

- Mild
- Moderate
- Severe

9.6.1.2.3 Causal relationship

The assessment of the causal relationship between an AE and the administration of treatment is a decision to be made by the investigator, who is a qualified physician, based on all information available at the time of the completion of the CRF.

Causality should be assessed separately for each study treatment as detailed in the CRF. If the investigator feels that the event cannot be firmly attributed to one of the study treatments (e.g. owing to a suspected underlying interaction), the same assessment will be documented for each study treatment.

The assessment is based on the question whether there was a “reasonable causal relationship” to the study treatment in question.

Possible answers are “yes” or “no”

An assessment of "no" would include:

1. The existence of a highly likely alternative explanation, e.g. mechanical bleeding at surgical site.

or

2. Non-plausibility, e.g. the subject is struck by an automobile when there is no indication that the drug caused disorientation that may have caused the event; cancer developing a few days after the first drug administration.

An assessment of "yes" indicates that that the AE is reasonably associated with the use of the study treatment.

Important factors to be considered in assessing the relationship of the AE to study treatment include:

- The temporal sequence from drug administration: The event should occur after the drug is given. The length of time from drug exposure to event should be evaluated in the clinical context of the event.
- Recovery on drug discontinuation (de-challenge): Subject's response after de-challenge should be considered in view of the usual clinical course of the event in question.
- Underlying, concomitant, intercurrent diseases:
  Each event should be evaluated in the context of the natural history and course of the disease being treated and any other disease the subject may have.
- Concomitant medication or treatment:
  The other drugs the subject is taking or the treatment the subject receives should be examined to determine whether any of them might have caused the event in question.
- Known response pattern for this class of drug: Clinical/preclinical
- Exposure to physical and/or mental stresses: The exposure to stress might induce adverse changes in the recipient and provide a logical and better explanation for the event
- The pharmacology and pharmacokinetics of the study treatment:
  The pharmacokinetic properties (absorption, distribution, metabolism and excretion) of the study treatment, coupled with the individual subject's pharmacodynamics should be considered.
- The assessment is not possible

Causal relationship to protocol-required procedures

The assessment of a possible causal relationship between the AE and protocol-required procedure(s) is based on the question whether there was a "reasonable causal relationship" to protocol-required procedure(s).

Possible answers are "yes" or "no"

9.6.1.2.4 Action taken with study treatment

Any action on study treatment to resolve the AE is to be documented using the categories listed below.

- Drug withdrawn
- Dose not changed
- Not applicable
- Unknown

9.6.1.2.5 Other specific treatment(s) of adverse events

- None
- Remedial drug therapy
- Other

9.6.1.2.6 Outcome

The outcome of the AE is to be documented as follows:

- Recovered/resolved
- Recovering/resolving
- Recovered/resolved with sequelae
- Not recovered/not resolved
- Fatal
- Unknown

9.6.1.3 Assessments and documentation of adverse events

The investigator has to record on the respective eCRF pages all adverse events occurring in the period between the signing of the informed consent and the end of study; after the end of the study there is no requirement to actively collect AEs including deaths. The type of information that should be assessed and recorded by the investigator for each AE is listed in Section 9.6.1.2.

"Death" should not be recorded as an AE on the AE page. Instead, "death" is the outcome of underlying AE(s).

For all serious adverse events (SAEs) the sponsor has to carry out a separate assessment for expectedness, seriousness and causal relationship to study drug.

The following events should **not be reported as AEs/SAEs**, unless (i) they are specifically considered as such by the investigator, according to the following conditions, or (ii) they lead to withdrawal of a subject from the study. This is to avoid redundancy and/or inconsistent reporting of AEs as these data may already be recorded in the CRF or subject's eDiary.

- **Ovarian cysts**: An ovarian cyst should only be reported as an AE if it is felt to be non-physiologic (at the discretion of the investigator). Ultrasound examinations will not be routinely scheduled as part of this study but may be performed by the investigator if thought to be necessary to evaluate symptoms of an ovarian cyst or other pelvic pathology. If an ovarian cyst is diagnosed, follow-up should be in accordance with the investigator's standard practice.

- **Findings on the bleeding diary:** Uterine bleeding (including intracyclic bleeding and absence of bleeding) should be recorded as an AE only if:
    - it leads to study discontinuation
    - it leads to therapeutic or diagnostic procedures
    - it is regarded as SAE
    - it shows a clinically significant worsening during the study that, in the judgment of the investigator, is not consistent with the expected clinical course, or are specifically reported as AEs by the subject.

9.6.1.4 Reporting of serious adverse events

The definition of serious adverse events (SAEs) is given in Section 9.6.1.1. Each SAE must be followed up until resolution or stabilization by submission of updated reports to the designated recipient.

Investigator's notification of the sponsor

All investigators will be thoroughly instructed and trained on all relevant aspects of the investigator's reporting obligations for SAEs. This information, including all relevant contact details, is summarized in the investigator site file. This information will be updated as needed.

The investigator must report immediately (within 24 hours of the investigator's awareness) all SAEs occurring during the observation period defined in Section 9.6.1.3 to the recipient detailed in the instructions for SAE reporting included in the Investigator File. For this, an AE page in the CRF as well as the complementary pages provided in the Investigator File must be completed for each SAE.

SAEs occurring after the protocol-defined observation period will be processed by the sponsor according to all applicable regulations.

Notification of the IECs / IRBs

Notification of the IECs / IRBs about all relevant events (e.g. SAEs, suspected, unexpected, serious adverse reactions [SUSARs]) will be performed by the sponsor and/or by the investigator according to all applicable regulations.

Notification of the authorities

The processing and reporting of all relevant events (e.g. SAEs, SUSARs) to the authorities will be done by the sponsor according to all applicable regulations.

Sponsor's notification of the investigational site

The sponsor will inform all investigational sites about reported relevant events (e.g. SUSARs) according to all applicable regulations.

9.6.1.5 Expected adverse events

For this study, the applicable reference document is the most current version of the investigator's brochure (IB).

Overview listings of frequent events that have occurred so far in the clinical development are shown in the current IB. If relevant new safety information is identified, the information will be integrated into an update of the IB and distributed to all participating sites.

The expectedness of AEs will be determined by the sponsor according to the applicable reference document and according to all local regulations.

9.6.2 Pregnancies

The occurrence of pregnancies is the primary efficacy variable in this study. For further details, please refer to Section 9.4.1.

9.6.3 Further safety

9.6.3.1 Vital signs and weight

Vital signs and body weight will be measured according to the schedule presented in Table 9–1.

Vital signs will include heart rate (for 1 minute, after 5 minutes in the sitting position) and systolic and diastolic blood pressure (after 5 minutes in the sitting position).

In case of clinically relevant deviations in vital signs, the values are to be confirmed by repeated measurement before documentation.

The subject will be weighed on a scale, without shoes, and dressed with approximately similarly heavy clothes at each appropriate visit (see Table 9–1).

9.6.3.2 Physical examination

A general physical examination should be conducted in accordance with the investigator's standard practice at the time points shown in Table 9–1.

Any physical examination finding, symptom, or disease observed prior to signing the ICF should be recorded as medical history. After signing the ICF, any deterioration or new physical examination finding, symptom, or disease should be recorded as an AE/SAE.

Abnormal physical examination findings are recorded either as medical history or as adverse events (see Section 9.6.1.1).

9.6.3.3 Gynecological examination

Gynecological examination will be performed at visits specified in Table 9–1. During the gynecological examination, the investigator will examine the following:

- Breasts
- Vulva
- Vagina
- Cervix

- Uterus
- Ovaries

Any gynecological examination finding, symptom, or disease observed prior to signing of the ICF should be recorded as medical history. After signing of the ICF, any deterioration or new gynecological examination finding, symptom, or disease should be recorded as an AE/SAE (see Section 9.6.1.1 and 9.6.1.3).

Please note that transvaginal ultrasound is not part of the gynecological examination, please see also Section 9.6.3.8.

9.6.3.4 Pregnancy test

A urine pregnancy test (urine hCG) will be performed at every visit as presented in Table 9–1. In case of a suspected pregnancy at screening or baseline visits, the subject must be withdrawn from the study and is considered a screening failure. If a pregnancy occurs during the study treatment period (i.e. after the baseline visit), subjects should immediately contact the investigator for an unscheduled visit (for reporting of pregnancies, see also Section 9.4.1). During the course of the study, additional urine hCG testing should be performed if there is clinical suspicion of pregnancy at any time.

In addition to the urine hCG tests performed by the site at each study visit, subjects will be provided with home urine pregnancy tests to be used whenever a pregnancy might be suspected.

If results of a home pregnancy test are positive or if a subject is unsure whether she is pregnant after performing the test, she should immediately contact the study site to schedule a visit and have a confirmatory test performed.

In the event of a positive urine hCG result, pregnancy should be confirmed according to the local standard of care (e.g., serum hCG testing).

9.6.3.5 Cervical smear

Cervical smear should be obtained following the standard practice of the study site at the screening visit (Visit 1) if there is no documented normal result available within the previous 6 months. Samples will be sent to the central laboratory for analysis. The cervical smear needs to be normal or clinically insignificant not requiring further follow up. Any abnormality detected prior to signing the ICF should be recorded as medical history. Subjects with ASCUS can be included in the study if they have an HPV DNA test that, according to the standards of the local laboratory, is negative for high-risk HPV. Cervical smear may be repeated once during the screening period if screening results are abnormal. After signing of the informed consent form, any deterioration or new abnormality should be recorded as an AE.

9.6.3.6 Test for Chlamydia

This section was changed in Amendment 1, see Section 15.1.1.14.

The subject will be tested for *Chlamydia* at the screening visit. *Chlamydia* tests must be performed using a highly accurate test method (e.g. the polymerase chain reaction [PCR] test, an example of nucleic acid amplification tests [NAAT]) in the central laboratory.

A single repeat test is permissible if the screening results are positive. If the test result is positive, the subject must also be tested for gonorrhea. Gonorrhea tests must also be performed using a highly accurate test method that meets the standards of GLP. A subject with an active genital infection may not be assigned to study treatment until the infection has been successfully treated (see Section 6.2, Exclusion criterion 4).

During the study, if a subject is found to have cervicovaginitis but not pelvic inflammatory disease, she should be treated keeping Mirena in situ and according to local medical standards.

9.6.3.7 Safety laboratory tests

This section was changed in Amendment 1, see Section 15.1.1.3.

Only blood samples analyzed at the central laboratory will be considered for analysis. The name and address for the central lab service provider can be found in the documentation supplied by the vendor. For a given laboratory parameter, the acceptable values for inclusion would consist of values within the reference ranges, measured at baseline, as provided in the Covance Central Laboratory Services (CCLS) Manual for Bayer Protocol 18649 (Covance Project #: 518179). The safety laboratory tests may be repeated once during the screening period if laboratory values are outside the inclusion range and assessed as clinically relevant.

The basic safety laboratory includes:

Hematology: leukocytes, erythrocytes, hemoglobin, hematocrit, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), platelets, neutrophils, eosinophils, basophils, lymphocytes, monocytes, glycosylated hemoglobin (HbA1c)

Serum chemistry: creatinine, chloride, potassium, sodium, calcium, total protein, albumin, total cholesterol, high density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol, triglycerides, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transpeptidase, alkaline phosphatase, and total bilirubin.

Follicle-stimulating hormone (FSH) (only at screening)

Urinalysis includes pH, urobilinogen, blood/hemoglobin, total protein, ketone, bilirubin, nitrite, glucose, and leukocytes.

Repeat sampling and testing is permitted in the event the sample quality is deemed poor or inadequate.

In the event of implausible results, the laboratory may measure additional parameters to assess the quality of the sample (e.g. clotted or hemolyzed) and to verify the results. The results from such additional analyses may neither be included in the clinical database of this

study nor evaluated further. If the results are relevant, the investigator will be informed to determine follow-up activities outside of this protocol.

9.6.3.8 Presence of Mirena removal threads

This section was changed in Amendment 1, see Section 15.1.1.22.

The presence of the removal threads will be checked at each study visit and recorded in the eCRF.

The investigator will perform pelvic examinations at each study visit to verify the presence of the Mirena removal threads in the appropriate location in the cervical os. If the presence of the removal threads cannot be verified, transvaginal ultrasound (TVUS) is to be performed to verify that the Mirena is in the appropriate intrauterine location and to exclude expulsion or perforation. The subject should be instructed to periodically check the threads by feeling for the threads at the top of the vaginal canal and if, at any time of the study, a subject suspects that the Mirena may have been expelled, she should contact the investigator and the investigator should assess the need for an unscheduled visit to evaluate the location of the Mirena. The subject should be instructed to use non-hormonal back-up method of contraception until it is confirmed that the Mirena is in the proper location.

Subject is **in compliance** with Mirena when:

- Threads are visible, or,
- Threads are not visible (or not checked) but TVUS performed to localize the Mirena shows Mirena to be “In situ” or “Displaced intrauterine”.

Subject is **non-compliant** with Mirena when:

- Threads are not visible, and,
- TVUS performed to localize Mirena shows that the IUS is “Partially or totally expelled into vagina or cervical canal”, “Cervical perforation”, “Myometrial perforation”, “Localization in the peritoneal cavity”, or “Absent”.
- Threads are visible, but TVUS is performed for other reason(s) and Mirena localization is recorded as “Partially or totally expelled into vagina or cervical canal”, “Cervical perforation”, “Myometrial perforation”, “Localization in the peritoneal cavity”.

Non-compliance with Mirena necessitates discontinuation of the subject from the study. In case the IUS is partially expelled, it needs to be removed. In case perforation has occurred, the IUS needs to be removed using appropriate procedures.

9.6.3.9 Expulsion of Mirena

Total or partial expulsion of the Mirena **will be reported as an AE or SAE, as appropriate** (i.e. meets the criteria for an SAE as specified in Section 9.6.1.1).

Total expulsion is confirmed if Mirena is observed in the vagina, it is not shown in the uterine cavity by ultrasound, and/or the subject confirms that the system was expelled. If, upon pelvic examination, the removal thread(s) cannot be seen, expulsion should be considered and an ultrasound must be performed. Possibilities of cervical or uterine perforations may be

excluded by ultrasound, x-ray or hysteroscopy before making a final diagnosis of total expulsion.

Partial expulsion is diagnosed if the Mirena can be partially seen in the vagina or is displaced in the cervical canal. If Mirena is partially expelled, it must be removed.

Upon total or partial expulsion of Mirena, the subject must discontinue study treatment and the study.

9.6.3.10 Perforation by Mirena

All perforations (cervical or myometrial perforations or perforations resulting in Mirena localization in the peritoneal cavity) **will be reported as SAEs**.

If a perforation is diagnosed, Mirena must be removed (this may require further intervention such as hysteroscopy or laparoscopy) and the subject must discontinue study treatment and the study.

9.6.3.11 Pelvic inflammatory disease

All cases of pelvic inflammatory disease (PID) **will be reported as an AE or SAE**, as appropriate.

For the purposes of this study, a diagnosis of pelvic inflammatory disease will be based on the following criteria:

- Presence of tenderness on pelvic examination **and**
- Current lower abdominal pain **and**
- At least 2 of the following findings:
  - Purulent or abnormal vaginal discharge
  - Increased serum C-reactive protein (≥ 30 mg/L)
  - Increased body temperature (≥ 38°C)
  - Typical findings of laparoscopy, if other clinical evidence is controversial
  - Evidence of causative pathogen (e.g., *Chlamydia trachomatis* or *Neisseria gonorrhea*) in the cervical canal

If pelvic inflammatory disease is not successfully treated, Mirena must be removed and the subject must discontinue the study.

The pelvic inflammatory disease eCRF and AE eCRF will be completed in all cases of pelvic inflammatory disease. If classified as an SAE, the appropriate forms will be completed and the sponsor's local pharmacovigilance unit notified. Details regarding notification to the Sponsor's local pharmacovigilance unit are provided in Section 9.6.1.4.

9.6.3.12 Uterine bleeding

This section was changed in Amendment 1, see Section 15.1.1.19.

The occurrence of uterine bleeding will be recorded every day during the treatment phase using eDiaries provided by the sponsor. The recording will start at the baseline visit and will

be continued daily until Mirena is removed. Subjects are asked to rate their uterine bleeding in the past 24 hours on a daily basis according to the bleeding intensity definitions presented in Table 9–3.

Table 9–3 Uterine bleeding – bleeding intensity definitions – amended

Category	Intensity	Bleeding Intensity Code	Definition
None	None	1	No uterine bleeding
Spotting	Spotting	2	Less than associated with normal menstruation relative to the woman's experience, with no need for sanitary protection except for panty liners
Bleeding	Light	3	Less than associated with normal menstruation relative to the woman's experience, with need for sanitary protection
	Normal	4	Like normal menstruation relative to the woman's experience
	Heavy	5	More than normal menstruation relative to the woman's experience

9.7 Other procedures and variables

9.7.1 eDiary

This section was changed in Amendment 1, see Section 15.1.1.23.

Patient-reported outcomes (PROs) will be collected using an electronic diary (eDiary). Recording of the uterine bleeding is the main part of the eDiary. The use of back-up contraception will also be documented within the same eDiary. Recall time will be 72 hours.

Subject will enter her data daily into the eDiary. The use of the eDiary will be explained in detail in a site manual, and the site personnel will train the subject on how to use the device at the baseline visit. At all the following visits (see Table 9–1), the eDiary entries will be checked and documented by the study site personnel for completeness. The investigator or designee and the on-site CRA will regularly review the eDiary entries via an internet-based application. The eDiary device will be returned at the end-of-treatment visit (Visit 8).

9.7.2 Continuing need of contraception

During each study visit, the subject will be asked about her continuing need for contraception since the last contact/visit.

9.7.3 Mirena removal – assessment of the ease of the procedure (by investigator) and pain during the removal (by subject)

The assessments described here have been developed by the sponsor specifically for use in sponsor's IUS studies.

The purpose of this assessment is to provide a subjective evaluation of the pain, if any, on removal of Mirena. The subject will assess the pain she experienced during Mirena removal as none, mild, moderate or severe and this will be recorded by the investigator in the eCRF. To avoid redundancy, any removal pain reported by the subject should not be recorded as an AE unless specifically considered as such by the investigator.

The ease of Mirena removal will be evaluated by the investigator as easy, slightly difficult or very difficult, and recorded in the eCRF. The use of painkillers, (para)cervical blockade or dilation will be documented by the investigator in the eCRF as concomitant medication.

Information regarding the Mirena removal procedure will be collected on the Mirena Removal Ease (by investigator) and Pain (by subject) eCRFs.

Please see also Section 7.6 about reporting of technical complaints.

9.7.4 Subject satisfaction with Mirena

This section was changed in Amendment 1, see Section 15.1.1.1.

At baseline visit, visit 4, 6 and at the end of the treatment (EOT, visit 8) (see also Table 9–1), the subject is asked to evaluate her satisfaction with the Mirena on a 5-point scale as very satisfied, somewhat satisfied, neither satisfied or dissatisfied, dissatisfied or very dissatisfied. Information regarding the subject satisfaction will be documented by the investigator in eCRF.

9.7.5 Back-up contraception

Subjects will be required to record the use of any back-up contraception (e.g. use of condoms for protection against sexually transmissible infections [STIs]) in their diaries. The only back-up contraception allowed during study treatment is the use of a barrier method (e.g. condoms).

Please see also Section 7.4.1

9.8 Appropriateness of procedures / measurements

The procedures chosen to measure the variables of this study are standard and/or widely used, and generally recognized as reliable, accurate, and relevant.

10. Statistical methods and determination of sample size

10.1 General considerations

Statistical analyses will be conducted by or under the supervision of the sponsor's study statistician, except for the analysis of PK/PD data, which will be planned, performed and reported under the supervision of the sponsor´s pharmacometrics group. Statistical analysis will be performed using SAS; the version used will be specified in the statistical analysis plan.

10.2 Analysis sets

This section was changed in Amendment 1, see Sections 15.1.1.1, 15.1.1.18 and 15.1.1.25.

The documentation of important deviations and the assignment of subjects to analysis sets will be performed according to the CRO's applicable Standard Operating Procedures and/or Instruction Manuals.

The following statistical analysis sets will be defined:

Full analysis set (FAS):
All women who completed the baseline visit of the study

Primary analysis set Year 6 (PAS year 6):

All women in the FAS with an age of 35 years or younger at baseline visit (i.e. an age of 36 or younger at end of year 6)

Primary analysis set Year 7 (PAS year 7):
All women in the FAS with an age of 34 years or younger at baseline visit (i.e. an age of 36 or younger at end of year 7)

Primary analysis set Year 8 (PAS year 8):
All women in the FAS with an age of 33 years or younger at baseline visit (i.e. an age of 36 or younger at end of year 8)

***Safety analysis set (SAF)*:**
All women who completed the baseline visit of the study, analyzed for the FAS.

The age at baseline (required for PAS year 6, PAS year 7 and PAS year 8) will be used as recorded at the baseline visit 2.

10.3 Variables and planned statistical analyses

This section was changed in Amendment 1, see Section 15.1.1.26.

In order to allow some flexibility, the baseline visit is planned to take place 14 to 0 days before the end of Year 5 of Mirena use (see Table 9–1). As a consequence, it is expected there will be various subjects with that baseline visit taking place prior to the start of 'extension treatment period', i.e. Day 1 of Year 6 of Mirena use.

Variables collected on an ongoing basis will primarily be analyzed for the 'extension treatment period' starting at Day 1 of Year 6 of Mirena use, i.e., data collected between the baseline visit and Day 1 of Year 6 of Mirena use will be excluded:

- Primary efficacy variable, i.e. occurrence of pregnancies (section 10.3.2.1)
- Main safety variable, i.e. adverse events (section 10.3.2.3.1)
- Uterine bleeding / bleeding pattern (section 10.3.2.3.2)

Variables collected at pre-specified visits/timeframes only will be analyzed per visit (unless otherwise stated):

- Secondary efficacy variable, i.e. menstrual blood loss (section 10.3.2.2)

- Other safety variables, not listed above (section 10.3.2.3.3)
- Other variables (section 10.3.2.4)

More details will be provided in the statistical analysis plan.

10.3.1 Variables

10.3.1.1 Efficacy variables

10.3.1.1.1 Primary efficacy variable

This section was changed in Amendment 1, see Section 15.1.1.1 and 15.1.1.26.

The primary efficacy variable is the occurrence of pregnancy within years 6 thru 8 of Mirena use. However, for the analysis after 6 years of Mirena use, the primary efficacy variable is the occurrence of pregnancy within year 6 of Mirena use, and for the analysis after 7 years, the primary efficacy variable is the occurrence of pregnancy within years 6 thru 7 of Mirena use.

The Pearl Index (PI) is defined as the number of pregnancies per 100 woman years. The Pearl Index will be analyzed for the 'extension treatment period' starting at Day 1 of Year 6 of Mirena use, i.e., exposure and pregnancies between the baseline visit and Day 1 of Year 6 of Mirena use will be excluded. The following PIs will be calculated:

- '1-year PI' (sixth year)', PI obtained in the sixth year of treatment, i.e., number of pregnancies that occurred during the sixth year of treatment divided by time the women were under risk of getting pregnant in the sixth year of treatment.
- '2-year PI' (sixth and seventh year)', PI obtained in the sixth and seventh year of treatment, i.e., number of pregnancies that occurred during the sixth and seventh year of treatment divided by time the women were under risk of getting pregnant in the sixth and seventh year of treatment.
- '3-year PI' (sixth, seventh and eighth year)', PI obtained in the sixth, seventh and eighth year of treatment, i.e., number of pregnancies that occurred during the sixth, seventh and eighth year of treatment divided by time the women were under a risk of getting pregnant in the sixth, seventh and eighth year of treatment.

Furthermore, the following PI will be analyzed for the entire study period starting at baseline visit, i.e., exposure and pregnancies between the baseline visit and Day 1 of Year 6 of Mirena use will be included:

- 'Overall PI', PI obtained during the whole study, i.e., number of pregnancies that occurred during the entire study period starting at baseline visit divided by the time the women were under a risk of getting pregnant.

The exact rules regarding how the exposure time will be calculated are given in Section 10.3.2.1.

10.3.1.1.2 Secondary efficacy variables

Secondary efficacy variables are:

- Menstrual blood loss (MBL) during a 30-day period starting at the baseline visit and at the end of Years 6, 7 and 8. MBL will be measured by the alkaline hematin method. The assessment of this variable is restricted to women who had Mirena inserted for HMB.
- Categorized menstrual blood loss (MBL) (>= 80 ml per 30 days) at end of Year 6, 7 and 8. The assessment of this variable is restricted to women who had Mirena inserted for HMB.

10.3.1.2 Safety variables

This section was changed in Amendment 1, see Section 15.1.1.15 and 15.1.1.26.

The main safety variable is the incidence of treatment-emergent adverse events (both serious and non-serious). Treatment-emergent AEs are defined as any AEs occurring during the 'extension treatment period' starting at Day 1 of Year 6 of Mirena use.

Other safety variables are:

- Uterine bleeding / Bleeding pattern
- Vital signs and weight
- Cervical smear
- Test for Chlamydia
- Safety laboratory parameters
- Presence of Mirena removal threads
- Mirena expulsion rate
- Mirena perforation rate

10.3.1.3 Other variables

Other variables are:

- Pharmacokinetic parameters
- Residual LNG content
- Discontinuation rate
- Subject satisfaction
- Mirena removal: Ease and pain

10.3.2 Statistical methods

10.3.2.1 Analysis of the primary variable

This section was changed in Amendment 1, see Sections 15.1.1.1, 15.1.1.5, 15.1.1.7, 15.1.1.8, and 15.1.1.26.

The primary variable is the occurrence of pregnancy within years 6-8 of Mirena use. However, for the analysis after 6 years, the primary variable is the occurrence of pregnancy within year 6 of Mirena use, and for the analysis after 7 years, the primary variable is the occurrence of pregnancy within years 6 thru 7 of Mirena use.

Definitions for PIs are presented in Table 10–1.

Table 10–1 Definition of crude exposure times – *amended*

PI	Reason for end of study/ continuation status	Crude exposure time
1-year PI (6th year)	Total expulsion	Date, when expulsion was discovered – Date of Day 1 Year 6 +1
	Partial Expulsion/ Mirena removal	Date of Mirena removal – Date of Day 1 Year 6 +1
	Pregnancy	Date of conception – Date of Day 1 Year 6 +1
	Lost to Follow up	Maximum of (Date Mirena last known in situ – Date of Day 1 Year 6 +1; 1 day)
	Continues into 7th year of treatment	365 days
2-year PI (6th and 7th year)	Total expulsion	Date, when expulsion was discovered – Date of Day 1 Year 6 +1
	Partial Expulsion/ Mirena removal	Date of Mirena removal – Date of Day 1 Year 6 +1
	Pregnancy	Date of conception – Date of Day 1 Year 6 +1
	Lost to Follow up	Maximum of (Date Mirena last known in situ – Date of Day 1 Year 6 +1; 1 day)
	Continues into 8th year of treatment	730 days
3-year PI (6th, 7th and 8th year)	Total expulsion	Date, when expulsion was discovered – Date of Day 1 Year 6 +1
	Partial Expulsion/ Mirena removal	Date of Mirena removal – Date of Day 1 Year 6 +1
	Pregnancy	Date of conception – Date of Day 1 Year 6 +1
	Lost to Follow up	Maximum of (Date Mirena last known in situ – Date of Day 1 Year 6 +1; 1 day)

PI	Reason for end of study/ continuation status	Crude exposure time
	Continues into 9th year of treatment	Minimum of (1095 days; Date of EOT visit – Date of Day 1 Year 6 +1)
Overall PI	Total expulsion	Date, when expulsion was discovered – Baseline visit date +1
	Partial Expulsion/ Mirena removal	Date of Mirena removal – Baseline visit date +1
	Pregnancy	Date of conception – Baseline visit date +1
	Lost to Follow up	Maximum of (Date Mirena last known in situ – Baseline visit date +1; 1 day)
	Continued until EOT	Date of EOT visit – Baseline visit date +1

A pregnancy will be allocated to the time period(s) that are relevant for the calculation of the PIs described above, e.g., a pregnancy that occurs on day 400 will be relevant for the 7th year PI, the two years PI (6th and 7th year), the three years PI (6th, 7th and 8th year), and the overall PI. Pregnancies that occur before Day 1 Year 6 of Mirena use will not count for the 1-year PI, 2-year PI and 3-year PI. Pregnancies that occur after the Mirena was removed or an expulsion was realized will not count for any PI.

It should be noted that e.g., pregnancies that occur after partial expulsion, but before Mirena removal will count for the PIs.

Furthermore, it should be noted that pregnancies that occur within 7 days after the end of exposure will count for the PIs.

Exposure times to be subtracted:

Subjects who apply additional concomitant contraception are not in risk or are under a lower risk of getting pregnant than subjects who do not apply additional contraception. In case a subject uses concomitant contraceptive methods (e.g., condoms to prevent STD); the respective 28-day reference period(s) of additional contraceptive method use will be excluded from the exposure time, unless a pregnancy occurred in that 28-day reference period.

Primary analysis

The primary method for the evaluation of the occurrence of pregnancy is the Pearl index defined as the number of pregnancies per 100 women years.

The PIs and the corresponding 2-sided 95 % confidence interval (CI) will be calculated using the model specified below.

Mathematical model for the calculation of the PI:

By assuming that the number of pregnancies follows a Poisson-distribution, the point estimate and the 95 % CI for the PI can be calculated as follows:

$PI = x/E$,

lower 95 % confidence limit of PI = 0.5 x $\chi^2_{(0.025,\ 2x)}$ /E

upper 95 % confidence limit of PI = 0.5 x $\chi^2_{(0.975,\ 2(x+1))}$ /E

where x = number of pregnancies,

E = exposure in 100 woman years (one woman year is 365 days of treatment exposure),

$\chi^2_{(alpha,df)}$ is the alpha quantile from χ^2-distribution with df degrees of freedom.

The primary analysis set will be the PAS Year 6 (for the analysis after 6 years), the PAS Year 7 (for the analysis after 7 years) and the PAS Year 8 (for the final analysis after 8 years), respectively. Furthermore, analyses will be repeated for the FAS.

Secondary analysis

In order to fulfill the European guideline EMEA-'Guideline on clinical investigation of steroid contraceptives in women' (EMEA/CPMP/EWP/519/ Rev1, July 2005.), the cumulative failure rate, i.e., the probability of getting pregnant will be calculated using the Kaplan Meier method in addition to the calculation of PIs.

Sensitivity analyses

The usual assumption for the calculation of the PI is a constant hazard for the event of becoming pregnant over time. As this cannot necessarily be assumed for the study treatment of this study, PIs will be calculated *per year*, as sensitivity analyses.

10.3.2.2 Analysis of the secondary variables

10.3.2.2.1 Menstrual blood loss

This section was changed in Amendment 1, see Section 15.1.1.10.

Menstrual blood loss (MBL) at beginning of year 6, end of year 6, end of year 7, and end of year 8 of Mirena treatment will be presented by descriptive statistics. Furthermore, change from baseline (=beginning of year 6) will be presented.

The basis for this analysis is the data on MBL assessed by the alkaline hematin method (see section 9.4.2). If a woman has documented in the eDiary (see section 9.7.1) that no bleeding occurred during one of the 30-day time periods considered for collection of sanitary products, the MBL will be assumed to be zero in that time period. The handling of partial or missing data (i.e. data on sanitary products and/or bleeding intensities) and detailed imputation rules will be described in the statistical analysis plan.

This analysis will be conducted in the FAS in the HMB subgroup, i.e. women who had Mirena inserted for both contraception and HMB.

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Success will be concluded regarding this endpoint if less than 20% of the women in the HMB subgroup have a clinical change in bleeding profile regarding HMB (according to the definition above) and the upper limit of the corresponding 95% Clopper-Pearson confidence interval is equal to or less than 35%.

This analysis will be conducted in the FAS in the HMB subgroup, i.e. women who had Mirena inserted for both contraception and HMB.

10.3.2.3 Analysis of safety variables

This section was changed in Amendment 1, see Section 15.1.1.15 and 15.1.1.26.

All safety variables will be analyzed based on the SAF.

The main safety variable is the incidence of treatment-emergent adverse events (both serious and non-serious). Treatment-emergent AEs are defined as any AEs occurring during the 'extension treatment period' starting at Day 1 of Year 6 of Mirena use.

10.3.2.3.1 Adverse events

All AEs will be classified using MedDRA. The latest available version at the time of coding will be used. The results will be summarized, at a minimum, on the level of system organ class (SOC) and preferred term (PT). Data will also be summarized according to intensity and investigator's causality assessment.

10.3.2.3.2 Bleeding pattern

This section was changed in Amendment 1, see Sections 15.1.1.10, 15.1.1.19, and 15.1.1.26.

Bleeding diary data during the 'extension treatment period' starting at Day 1 of Year 6 of Mirena use will be analyzed according to the sponsor's Best Practice Document entitled "Recording and evaluation of bleeding data". Bleeding diary data prior to the 'extension treatment period' will not be included in the analyses. The handling of partial or missing data and detailed imputation rules will be described in the statistical analysis plan.

Bleeding intensity will be recorded by the subject on a daily basis using the categories presented in Table 9–3 in section 9.6.3.12.

In addition to absolute number of bleeding days, bleeding/spotting episodes will also be assessed according to the sponsor's Bleeding Intensity Codes and the World Health Organization (WHO) definitions as provided in Table 10–2.

Table 10–2 Bleeding Intensity Codes and WHO Definitions for Bleeding Intensity – *amended*

Bleeding Intensity Codes	WHO Definitions	
2 - 5	Bleeding/spotting episode:	Day(s) with bleeding/spotting preceded and followed by at least 2 bleeding-free days.
2	Spotting-only episode:	Day(s) with spotting preceded and followed by at least 2 bleeding-free days.
1	Bleeding/spotting-free interval:	At least 2 days without bleeding/spotting preceded and followed by at least 1 bleeding/spotting day.

In addition to the WHO definitions, a **bleeding episode** is defined as day(s) with bleeding/spotting of which at least one day is of intensity 3 or higher, preceded and followed by at least 2 bleeding-free days.

In the following example (Table 10–3) of an assessment of bleeding episodes the above definitions are applied to determine whether the event consisted of a **single bleeding episode** or **multiple bleeding episodes**. In Table 10–3, each recorded bleeding event consists of 5 bleeding days. However, as shown and described, the pattern of bleeding determines whether the 5 days are considered as one or two bleeding episodes.

Based on daily data obtained from the electronic diary, the bleeding pattern will be reported using reference periods of 28 and 90 days. The first 28-day and 90-day reference period, respectively, will start at Day 1 of Year 6 of Mirena use. For each subject and for each period, the number of bleeding/spotting days and bleeding/spotting episodes will be calculated. If the bleeding intensity is recorded as light, normal or heavy, this will be considered as 'bleeding'.

For each subject and for each 28-day reference period and each 90-day reference period, the

following bleeding indices will be calculated:

- number of subjects with at least one bleeding/spotting day
- number of subjects with at least one bleeding (excluding spotting) day
- number of bleeding/spotting days
- number of bleeding days (excluding spotting)
- number of spotting only days
- number (mean length, maximal length, and range of length) of bleeding/spotting episodes
- number (mean length, maximal length, and range of length) of spotting only episodes (will only be calculated for those subjects who have at least 1 spotting-only episode)

Table 10–3 Example of an Assessment of Bleeding Episodes

A					1	2	3	4	5							one episode of 5 days
B					1	2			1	2	3					two episodes; one of 2 days, one of 3 days
C					1	2	3	4	5	6	7	8				one episode of 8 days
D					1	2	3			1	2	3				two episodes of 3 days each

■ Denotes bleeding □ Denotes no bleeding

Scenario A: one bleeding episode of 5 consecutive days; there is no bleeding/spotting-free interval

Scenario B: two bleeding episodes; there is a 2-day bleeding/spotting-free interval between the 2-day episode and the 3-day episode

Scenario C: one bleeding episode; although there are bleeding-free days between bleeding days, the definition of a bleeding/spotting-free interval requires 2 consecutive days

Scenario D: two bleeding episodes; although there is one bleeding-free day in the first 3-day episode, the definition of a bleeding/spotting-free interval requires 2 consecutive days. There is the required 2-day bleeding/spotting-free interval between the two 3-day episodes.

Furthermore, for each 90-day reference period the following bleeding indices were provided according to the WHO criteria:

- number of subjects with amenorrhea, defined as no bleeding/spotting throughout the reference period
- number of subjects with prolonged bleeding, defined as subjects with bleeding/spotting episodes lasting more than 14 days
- number of subjects with frequent bleeding, defined as subjects with more than 5 bleeding/spotting episodes
- number of subjects with infrequent bleeding, defined as subjects with 1 or 2 bleeding/spotting episodes
- number of subjects with irregular bleeding, defined as subjects with 3 to 5 bleeding/spotting episodes and less than 3 bleeding/spotting-free intervals of 14 days or more.
- number of subjects with normal bleeding / none of the above.

10.3.2.3.3 Other safety variables

All other safety variables will be analyzed descriptively using summary statistics or frequency tables as appropriate.

10.3.2.4 Other variables

10.3.2.4.1 Pharmacokinetic parameters

Pharmacokinetic data collected during the study will be analyzed descriptively.

Population PK analysis will be performed as described in a separate M&S Analysis Plan and reported in a separate M&S Report.

10.3.2.4.2 Residual LNG content

Residual LNG content will be analyzed descriptively.

10.3.2.4.3 Discontinuation rate

The discontinuation rate will be provided, calculated from the number of subjects with an expulsion, plus those who have Mirena removed due to partial expulsion or perforation, plus those who discontinue study treatment for other reasons. The Kaplan-Meier estimate will be used.

10.3.2.4.4 Subject satisfaction

The subject's satisfaction with the Mirena on a 5-point scale (very satisfied, somewhat satisfied, neither satisfied or dissatisfied, dissatisfied, very dissatisfied) will be summarized descriptively.

10.3.2.4.5 Mirena removal: ease and pain

The ease of Mirena removal (easy, slightly difficult, very difficult) will be summarized descriptively.

The pain during the removal (none, mild, moderate, severe) will be summarized descriptively.

10.4 Determination of sample size

The sample size calculation is not based on statistical considerations. It is targeted to have 200 women completing the 8th year of treatment with Mirena. With an estimated dropout rate of 15%, the total number of women to be enrolled into the study treatment phase would be 350.

In order to account for women excluded from the primary analysis due to age restrictions (i.e. women 34 years of age at baseline or older will not be included in the primary analysis set 'PAS year 8' for the final analysis after 8 years)[2], the total number of women to be enrolled into the study treatment phase is 360.

[2] It is assumed about 90% of women enrolled will be 18 to 32 years of age at screening, i.e. 10% of women will be 33 to 35 years old and accordingly less will be 34 to 35 years old.

Sample size characteristics regarding the analysis of the Pearl index:

This sample size will lead to an expected exposure (years 6 to 8 combined) of 832 women years (WY). Assuming a true Pearl index of 0.2,

- the upper limit of the 95% confidence interval for the PI (years 6-8) will not exceed 1 with a probability of 76%,
- the difference between the point estimate and the upper limit of the 95% confidence interval will not exceed 1 with a probability >99.9%.

Assuming a slightly higher true Pearl index of 0.3,

- the upper limit of the 95% confidence interval for the PI (years 6-8) will not exceed 1 with a probability of 55%,
- the difference between the point estimate and the upper limit of the 95% confidence interval will not exceed 1 with a probability >99.9%.

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10.5 Planned interim analyses

This section was changed in Amendment 1, see Section 15.1.1.1.

No formal interim analysis in the sense of a group sequential or adaptive design is planned. However, an analysis of the data is planned after Year 6, including all subjects who have prematurely discontinued or completed Visit 4, i.e. treated with Mirena for up to 6 years (1 year in the study). Another analysis of the data is planned after Year 7, including all subjects who have prematurely discontinued or completed Visit 6, i.e. treated with Mirena for up to 7 years (2 years in the study).

11. Data handling and quality assurance

11.1 Data recording

This section was changed in Amendment 1, see Section 15.1.1.23.

The data collection tool for this study will be eCRF; a validated electronic data capture system called RAVE. Subject data necessary for analysis and reporting will be entered/transmitted into a validated database or data system (e.g. CIE/TOSCA; SAS).

Data will be entered by site personnel into an internet based electronic data capture software system RAVE, which Covance has licensed from Medidata Solutions Worldwide. RAVE has been validated by Medidata Solutions Worldwide and Covance for use in its clinical studies. RAVE allows for the application of software logic to set-up data entry screens and data checks to ensure the completeness and accuracy of the data entered. Covance extensively applies the logic to ensure data are complete and reflect the requirements of the study. Queries resulting from the application of the software logic are resolved by site personnel. The data are stored at a secure host facility maintained by Medidata Solutions Worldwide and transferred on a periodic basis to Covance's internal computer system via a secure Virtual Private Network.

Access to RAVE is through a password-protected security system. All personnel are thoroughly trained before acquiring access to the system. Training records are maintained.

Personnel with access to RAVE are supported by a Service Desk to answer questions and ensure access is maintained such that data entry can proceed in a timely manner.

RAVE contains a system-generated audit trail that captures any changes made to a data field, including who made the change, why it was changed, and the date and time it was made. This information is available both at the investigator's site and at Covance.

Data entries are supported by source documents maintained for all subjects. A source document checklist will be used at the site to identify the source data for key data points collected and the monitor will work with the site to complete this.

Source documentation

The site must implement processes to ensure availability of all required source documentation. A source document checklist (not part of this protocol) will be used at the site to identify the source data for key data points collected and the monitor will work with the site to complete this.

It is the expectation of the sponsor that all data entered into the CRF has source documentation available at the site except for the data listed below which will be entered directly into the CRF; thus, these CRF data will be the source and no additional source documentation will be available. The data entered directly into the CRF is not needed for the subject's routine medical care.

- data fields to be completed directly in the eCRF:

- assessments on Mirena removal by subject (pain) and investigator (ease of removal), and
- subject's satisfaction with Mirena.

These will be entered into eCRF by the investigator.

eDiary data
The eDiary entries will be considered as primary source data.

Data recorded from screening failures

At minimum, the following data should be recorded in the CRF:

- Demographic information (subject number; year of birth / age; if applicable race / ethnicity)
- Date for Mirena insertion
- Indication for Mirena
- Reproductive and menstrual history
- Date of informed consent
- Relevant inclusion/exclusion criteria
- Reason for premature discontinuation
- Date of last visit.

These data will be transferred to the respective database.

For screening failures with an SAE or pregnancy (see also section 9.4.1), the following data should be collected in the CRF in addition to the data specified above:

- All information related to the SAE/pregnancies such as:
  - The SAE itself / pregnancy test evaluation page
  - Concomitant medication
  - Medical history
  - Other information needed for SAE complementary page

11.2 Monitoring

In accordance with applicable regulations, GCP, and sponsor's/CRO's procedures, monitors will contact the site prior to the start of the study to review with the site staff the protocol, study requirements, and their responsibilities to satisfy regulatory, ethical, and sponsor's requirements. When reviewing data collection procedures, the discussion will also include identification and documentation of source data items.

The sponsor/designee will monitor the site activity to verify that the:

- Data are authentic, accurate and complete.
  Supporting data may be requested (example: blood glucose readings to support a diagnosis of diabetes).
- Safety and rights of subjects are being protected
- Study is conducted in accordance with the currently approved protocol (including study treatment being used in accordance with the protocol)
- Any other study agreements, GCP, and all applicable regulatory requirements are met.

The investigator and the head of the medical institution (where applicable) agrees to allow the monitor direct access to all relevant documents.

11.3 Data processing

Data will be collected as described in Section 11.1. Clinical data management will be performed in accordance with applicable sponsor's/CRO's standards and data cleaning procedures. This is applicable for data recorded on eCRF as well as for data from other sources (e.g. laboratory, ePRO).

For data coding (e.g. AEs, medication), internationally recognized and accepted dictionaries will be used.

After its initial release for biometrical analysis, the clinical database is planned to be re-opened for the inclusion of the following additional data: e.g. pharmacokinetic data, residual content data and post study pregnancy tracking data.

11.4 Missing data

Most important is to avoid missing data, e.g. by monitoring in time for completeness (see Section 11.2) and investigators' training, especially by instructing them to motivate subjects to be compliant with the study protocol. If the subject is unable to come to on-site visit during the allotted timeframe, the visit may be documented via phone as described at Section 6.4.1 in order to collect as much data as possible. In addition, for completing the eDiary, 72-hour recall time is implemented to allow some flexibility for eDiary completion and to avoid missing eDiary data.

11.5 Audit and inspection

To ensure compliance with GCP and regulatory requirements, a member of the sponsor's (or a designated CRO's) quality assurance unit may arrange to conduct an audit to assess the performance of the study at the study site and of the study documents originating there. The investigator/institution will be informed of the audit outcome.

In addition, inspections by regulatory health authority representatives and IEC(s)/IRB(s) are possible. The investigator should notify the sponsor immediately of any such inspection.

The investigator/institution agrees to allow the auditor or inspector direct access to all relevant documents and allocate his/her time and the time of his/her staff to the auditor/inspector to

discuss findings and any issues. Audits and inspections may occur at any time during or after completion of the study.

11.6 Archiving

Essential documents shall be archived safely and securely in such a way that ensures that they are readily available upon authorities' request.

Patient (hospital) files will be archived according to local regulations and in accordance with the maximum period of time permitted by the hospital, institution or private practice. Where the archiving procedures do not meet the minimum timelines required by the sponsor, alternative arrangements must be made to ensure the availability of the source documents for the required period.

The investigator/institution notifies the sponsor if the archival arrangements change (e.g. relocation or transfer of ownership).

The investigator site file is not to be destroyed without the sponsor's approval.

The contract with the investigator/institution will contain all regulations relevant for the study center.

12. Premature termination of the study

The sponsor has the right to close this study (or, if applicable, individual segments thereof [e.g. treatment arms; dose steps; centers]) at any time, which may be due but not limited to the following reasons:

- If risk-benefit ratio becomes unacceptable owing to, for example,
    - Safety findings from this study (e.g. SAEs)
    - Results of any interim analysis
    - Results of parallel clinical studies
    - Results of parallel animal studies (on e.g. toxicity, teratogenicity, carcinogenicity or reproduction toxicity).
- If the study conduct (e.g. recruitment rate; drop-out rate; data quality; protocol compliance) does not suggest a proper completion of the trial within a reasonable time frame.

The investigator has the right to close his/her center at any time.

For any of the above closures, the following applies:

- Closures should occur only after consultation between involved parties. Final decision on the closure must be in writing.
- All affected institutions (e.g. IEC(s)/IRB(s); competent authority(ies); study center; head of study center) must be informed as applicable according to local law.
- All study materials (except documentation that has to remain stored at site) must be returned to the sponsor. The investigator will retain all other documents until notification is given by the sponsor for destruction.
- In the event of a partial study closure, ongoing subjects, including those in post study follow-up, must be taken care of in an ethical manner.

Details for individual subject's withdrawal can be found in Section 6.4.1.

13. Ethical and legal aspects

13.1 Investigators and other study personnel

This section was changed in Amendment 1, see Section 15.1.1.23

The name and contact information for the Sponsor's Study Medical Expert is provided in Section 1. The co-ordinating investigator who will be responsible for signing the CSR, is PPD (study center #PPD All other study personnel not included in this section are identified in a separate personnel list (not part of this clinical study protocol) as appropriate. This list will be updated as needed; an abbreviated version with personnel relevant for the centers will be available in each center's investigator site file.

Whenever the term 'investigator' is noted in the protocol text, it may refer to either the principal investigator at the site, or an appropriately qualified, trained and delegated individual of the investigational site.

The principal investigator of each center must sign the protocol signature page and must receive all required external approvals (e.g. health authority, ethics committee, sponsor) before subject recruitment may start at the respective center. Likewise, all amendments to the protocol must be signed by the principal investigator and must have received all required external approvals before coming into effect at the respective center.

A complete list of all participating centers and their investigators, as well as all required signature documents, will be maintained in the sponsor's study file.

The global sponsor of this study is identified on the title page of this protocol. If required by local law, local co-sponsors will be nominated; they will be identified on the respective country-specific signature pages.

13.2 Funding and financial disclosure

Funding

This study will be funded by its sponsor.

Financial disclosure

Each investigator (including principal and/or any sub investigators) who is directly involved in the treatment or evaluation of research subjects has to provide a financial disclosure according to all applicable legal requirements. All relevant documentation will be filed in the trial master file.

13.3 Ethical and legal conduct of the study

The procedures set out in this protocol, pertaining to the conduct, evaluation, and documentation of this study, are designed to ensure that the sponsor and investigator abide by Good Clinical Practice (GCP) guidelines and the guiding principles detailed in the Declaration of Helsinki. The study will also be carried out in keeping with applicable local law(s) and regulation(s).

Documented approval from appropriate IEC(s)/IRBs will be obtained for all participating centers/countries before start of the study, according to GCP, local laws, regulations and organizations. When necessary, an extension, amendment or renewal of the IEC/IRB approval must be obtained and also forwarded to the sponsor. The responsible unit (e.g. IEC/IRB, head of the study center/medical institution) must supply to the sponsor, upon request, a list of the IEC/IRB members involved in the vote and a statement to confirm that the IEC/IRB is organized and operates according to GCP and applicable laws and regulations.

Strict adherence to all specifications laid down in this protocol is required for all aspects of study conduct; the investigator may not modify or alter the procedures described in this protocol.

Modifications to the study protocol will not be implemented by either the sponsor or the investigator without agreement by both parties. However, the investigator or the sponsor may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to the trial subjects without prior IEC/IRB/sponsor approval/favorable opinion. As soon as possible, the implemented deviation or change, the reasons for it and if appropriate the proposed protocol amendment should be submitted to the IEC/IRB/head of medical institution/sponsor. Any deviations from the protocol must be explained and documented by the investigator.

Details on discontinuation of the entire study or parts thereof can be found in Section 12.

13.4 Subject information and consent

All relevant information on the study will be summarized in an integrated subject information sheet and informed consent form provided by the sponsor or the study center. A sample subject information and informed consent form is provided as a document separate to this protocol.

Based on this subject information sheet, the investigator or designee will explain all relevant aspects of the study to each subject prior to her entry into the study (i.e. before any examinations and procedures associated with the selection for the study are performed or any study-specific data is recorded on study-specific forms).

The investigator will also mention that written approval of the IRB/IEC has been obtained.

Each subject will be informed about the following aspects of premature withdrawal:

- Each subject has the right to withdraw from the study at any time without any disadvantage and without having to provide reasons for this decision.
- The subject's consent covers end-of-study examinations as specified in the visit description described in Sections 6.4 and 9.1 to be conducted after withdrawal of consent.
- The subject's data that have been collected until the time of withdrawal will be retained and statistically analyzed in accordance with the statistical analysis plan.
- Subject-specific data on the basis of material obtained before withdrawal may be generated after withdrawal (e.g. image reading, analysis of biological specimen such as blood, urine or tissues); these data would also be retained and statistically analyzed in accordance with the statistical analysis plan. The subject has the right to object to the generation and processing of this post-withdrawal data. The subject's oral objection may be documented in the subject's source data.

Each subject will have ample time and opportunity to ask questions.

Only if the subject voluntarily agrees to sign the informed consent form and has done so, may she enter the study. Additionally, the investigator will personally sign and date the form. The subject will receive a copy of the signed and dated form.

The signed informed consent statement is to remain in the investigator site file or, if locally required, in the patient's note/file of the medical institution.

In the event that informed consent is obtained on the date that baseline study procedures are performed, the study record or subject´s clinical record must clearly show that informed consent was obtained prior to these procedures.

The informed consent form and any other written information provided to subjects will be revised whenever important new information becomes available that may be relevant to the subject's consent, or there is an amendment to the protocol that necessitates a change to the content of the subject information and / or the written informed consent form. The investigator will inform the subject of changes in a timely manner and will ask the subject to confirm her participation in the study by signing the revised informed consent form. Any revised written informed consent form and written information must receive the IEC/IRB`s approval / favorable opinion in advance of use.

13.5 Publication policy and use of data

The sponsor has made the information regarding the study protocol publicly available on the internet at www.clinicaltrials.gov.

All data and results and all intellectual property rights in the data and results derived from the study will be the property of the sponsor who may utilize them in various ways, such as for submission to government regulatory authorities or disclosure to other investigators.

Regarding public disclosure of study results, the sponsor will fulfill its obligations according to all applicable laws and regulations. The sponsor is interested in the publication of the results of every study it performs.

The sponsor recognizes the right of the investigator to publish the results upon completion of the study. However, the investigator, whilst free to utilize study data derived from his/her center for scientific purposes, must obtain written consent of the sponsor on the intended publication manuscript before its submission. To this end, the investigator must send a draft of the publication manuscript to the sponsor within a time period specified in the contract. The sponsor will review the manuscript promptly and will discuss its content with the investigator to reach a mutually agreeable final manuscript.

13.6 Compensation for health damage of subjects / insurance

The sponsor maintains clinical trial insurance coverage for this study in accordance with the laws and regulations of the country in which the study is performed.

13.7 Confidentiality

All records identifying the subject will be kept confidential and, to the extent permitted by the applicable laws and/or regulations, will not be made publicly available.

Subject names will not be supplied to the sponsor. Only the subject number will be recorded in the CRF, and if the subject name appears on any other document (e.g. pathologist report), it must be obliterated before a copy of the document is supplied to the sponsor. Study findings stored on a computer will be stored in accordance with local data protection laws. As part of the informed consent process, the subjects will be informed in writing that representatives of the sponsor, IEC/IRB, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection laws.

If the results of the study are published, the subject's identity will remain confidential.

The investigator will maintain a list to enable subjects to be identified.

14. Reference list

This section was changed in Amendment 1, see Section 15.1.1.20.

1. McNicholas C, Swor E, Wan L, Peipert JF. Prolonged use of the etonogestrel implant and levonorgestrel intrauterine device: 2 years beyond Food and Drug Administration-approved duration. Am J Obstet Gynecol. 2017 Jan 29[Epub ahead of print].
2. Rowe P, Farley T, Peregoudov A, Piaggio G, Boccard S, Landoulsi S, Meirik O; IUD Research Group of the UNDP/UNFPA/WHO/World Bank Special Programme of Research; Development and Research Training in Human Reproduction. Safety and efficacy in parous women of a 52-mg levonorgestrel-medicated intrauterine device: a 7-year randomized comparative study with the TCu380A. Contraception. 2016 Jun;93(6):498-506. doi: 10.1016/j.contraception.2016.02.024. Epub 2016 Feb 23.

3. Sivin I, Stern J, Coutinho E, Mattos CER, El Mahgoub S, Diaz S et al. Prolonged intrauterine contraception: a seven-year randomized study of the levonorgestrel 20 mcg/day (LNG 20) and the Copper T380 Ag IUDS. Contraception 1991;44:473-80.
4. Hidalgo MM1, Hidalgo-Regina C, Bahamondes MV, Monteiro I, Petta CA, Bahamondes L. Serum levonorgestrel levels and endometrial thickness during extended use of the levonorgestrel-releasing intrauterine system. Contraception. 2009 Jul;80(1):84-9. doi: 10.1016/j.contraception.2009.01.004. Epub 2009 Feb 27.
5. Andersson K, Odlind V, Rybo G. Levonorgestrel-releasing and copper-releasing (Nova T) IUDs during five years of use: a randomized comparative trial. Contraception. 1994;49(1):56-72. PubMed PMID: 8137626.
6. A46796 Phase 2 CSR. Multi-center, open, randomized, dose finding phase II study to investigate for a maximum of three years ultra low dose levonorgestrel contraceptive intrauterine systems (LCS) releasing in vitro 12 µg/24 h and 16 µg/24 h of levonorgestrel compared to MIRENA in nulliparous and parous women in need of contraception. Bayer HealthCare AG, 51368 Leverkusen, Germany. Study No. 91412 (alias 308901), version 2.0. 14 SEP 2011.
7. B073 Clinical Study Report. Serum levonorgestrel concentration during 78 month use of LNG IUD. Schering. 22 Nov 1991.
8. B078 Clinical Study Report. Five-year clinical performance of the new formulation of the levonorgestrel intrauterine ystem and serum levonorgestrel concentration with the new formulation compared to that with the original one. Leiras 18 JAN 1999.
9. PH-37274 Phase 3 CSR. Multi-center, open-label, randomized study to assess the safety and contraceptive efficacy of two doses (in vitro 12 µg/24 h and 16 µg/24 h) of the ultra low dose levonorgestrel contraceptive intrauterine systems (LCS) for a maximum of 3 years in women 18 to 35 years of age and an extension phase of the 16 µg/24 h dose group (LCS16 arm) up to 5 years. Bayer HealthCare AG, 51368 Leverkusen, Germany. Study No. 91665 (alias 310442), version 2.0, 06 Aug 2015.
10. Heinemann K, Reed S, Moehner S, Minh TD. Risk of uterine perforation with levonorgestrel-releasing and copper intrauterine devices in the European Active Surveillance Study on Intrauterine Devices. Contraception. 2015 Apr;91(4):274-9.
11. A52238 Phase 3 CSR. Multi-center, open-label, randomized study to assess the safety and contraceptive efficacy of two doses (in vitro 12 µg/24 h and 16 µg/24 h) of the ultra low dose levonorgestrel contraceptive intrauterine systems (LCS) for a maximum of 3 years in women 18 to 35 years of age and an extension phase of the 16 µg/24 h dose group (LCS16 arm) up to 5 years. Bayer HealthCare AG, 51368 Leverkusen, Germany. Study No. 91665 (alias 310442), version 2.0, 06 Aug 2015.
12. Heikinheimo O, Inki P, Schmelter T, Gemzell-Danielsson K. Bleeding pattern and user satisfaction in second consecutive levonorgestrel-releasing intrauterine system users: results of a prospective 5-year study. Hum Reprod. 2014 Jun;29(6):1182-8. doi: 10.1093/humrep/deu063. Epub 2014 Mar 28.

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15. Protocol amendments

15.1 Amendment 1 – dated 20 SEP 2017

Amendment 1 is the first global amendment. The following is an overview of the changes made to the original Protocol Version 1.0.

This amendment describes the assessments and statistical analyses needed to support a submission with 6-year efficacy and safety data to extend the duration of Mirena use to up to 6 years. In addition, protocol has been revised in order to consider the comments and feedback from the FDA (received 31 JAN 2017 and 12 JUL 2017). Also, minor edits and clarifications that were not previously identified in the original protocol were included in this amendment.

15.1.1 Overview of the changes to the study

15.1.1.1 Modification 1: Addition of the 6-year analysis and the required assessments needed for the analyses at Year 6

Rationale: To be able to submit the data to the FDA after 6 years of Mirena use.

List of protocol sections affected by this modification:

- Section 5 Study design
- Section 9.1 Tabular schedule of evaluations
- Section 9.2.5 12-month visit – Visit 4 (End of Year 6 of Mirena use)
- Section 9.7.4 Subject satisfaction with Mirena
- Section 10.2 Analysis sets
- Section 10.3.1.1.1 Primary efficacy variable
- Section 10.3.2.1 Analysis of the primary variable
- Section 10.3.2.2.2 Categorized menstrual blood loss (MBL) (<80ml / 30 days)
- Section 10.5 Planned interim analyses

15.1.1.2 Modification 2: Guidance about number of 34- or 35-year old women to be included into the screening period

Rationale: In order to ensure sufficient sample size for the final Pearl Index analysis (i.e. targeted 350 women aged 33 years or younger at baseline visit / aged 36 years or younger at the end of Year 8), screening of women who are 34 or 35 years old will be closed, once 10 women in this age group have completed the baseline visit.

List of protocol sections affected by this modification:

- Section 6 Study population

15.1.1.3 Modification 3: Information on inclusion range for laboratory values added

Rationale: As requested by the FDA

List of protocol sections affected by this modification:

- Section 6.2 Exclusion criteria
- Section 9.6.3.7 Safety laboratory tests

15.1.1.4 Modification 4: Revision of the criteria for mandatory withdrawal from the study

Rationale: Subject must be withdrawn if stroke, myocardial infarction, uterine malignancy and cervical malignancy occur during the study; requested by the FDA.

List of protocol sections affected by this modification:

- Section 6.4.1 Withdrawal

15.1.1.5 Modification 5: Clarification on counting of pregnancies with the estimated date of conception within 7 days after the end of Mirena treatment for the Pearl Index calculation

Rationale: As requested by the FDA

List of protocol sections affected by this modification:

- Section 9.4.1.2 Pregnancies occurring after the end of study treatment
- Section 10.3.2.1 Analysis of the primary variable.

15.1.1.6 Modification 6: Clarification of the post-treatment pregnancy tracking process (PTPT)

Rationale: To better distinguish the PTPT process-related data from the post-treatment pregnancy data collected at the 3-week FUP contact.

List of protocol sections affected by this modification:

- Section 9.2.10 3-week follow-up call (EOS)
- Section 9.2.11 3-month follow-up contact for post-study pregnancies
- Section 9.2.12 12-months follow-up contact for return-to-fertility
- Section 9.4.1.1 Pregnancies during the study
- Section 9.4.1.2 Pregnancies occurring after the end of study treatment

15.1.1.7 Modification 7: Clarification and correction of terms used in the definitions for calculation of crude exposure time

Rationale: As requested by the FDA.

List of protocol sections affected by this modification:

- Section 10.3.2.1 Analysis of the primary variable

15.1.1.8 Modification 8: Clarification of excluded exposure time due to back-up contraception use

Rationale: As requested by the FDA.

List of protocol sections affected by this modification:

- Section 10.3.2.1 Analysis of the primary variable.

15.1.1.9 Modification 9: Addition of sensitivity analysis for PI

Rationale: As requested by the FDA.

List of protocol sections affected by this modification:

- Section 10.3.2.1 Analysis of the primary variable.

15.1.1.10 Modification 10: Addition of a reference to the statistical analysis plan regarding handling of partial or missing data

Rationale: To provide guidance on how to handle missing or partial data, i.e. missing bleeding intensities to be recorded by the subject in the eDiary and/or missing and partial data on sanitary products to be collected by the subject.

List of protocol sections affected by this modification:

- Section 10.3.2.2.1 Menstrual blood loss
- Section 10.3.2.3.2 Bleeding pattern.

15.1.1.11 Modification 11: Clarification of the definition of clinical change in bleeding profile regarding HMB and of the proportion of subjects with clinical change in bleeding profile regarding HMB

Rationale: To clarify when clinical change in bleeding profile regarding HMB will be concluded, to add the stricter success criterion (i.e. upper confidence limit ≤ 35%) for this endpoint as requested by FDA and to provide more details on the nominator and denominators used to calculate the proportion of subjects with clinical change in bleeding profile regarding HMB.

List of protocol sections affected by this modification:

- Section 10.3.2.2.2 Categorized menstrual blood loss (MBL) (<80ml / 30 days).

15.1.1.12 Modification 12: Change in exclusion criterion about simultaneous participation in other trials

Rationale: Study subjects can participate in observation trials while in the study. To allow this, the wording in exclusion criterion #22 is revised accordingly.

List of protocol sections affected by this modification:

- Section 6.2 Exclusion criteria.

15.1.1.13 Modification 13: Withdrawal from study if heavy menstrual bleeding returns

Rationale: Investigator should consider if a subject should be withdrawn from the study in case heavy menstrual bleeding returns during the study

List of protocol sections affected by this modification:

- Section 6.4.1 Withdrawal

15.1.1.14 Modification 14: Reference to a local laboratory removed from the text.

Rationale: Mistake in the original protocol.

List of protocol sections affected by this modification:

- Section 9.6.3.6 Test for chlamydia.

15.1.1.15 Modification 15: Revised terminology of the adverse events to be included in the main safety analysis, and correction of the list of other safety variables.

Rationale: To ensure consistent wording across different studies, terminology of adverse events to be included in the main safety analysis was revised from “post-baseline” to “treatment-emergent”. It was a mistake in the original protocol in the list of other safety variables.

List of protocol sections affected by this modification:

- Section 10.3.1.2 Safety variables
- Section 10.3.2.3 Analysis of safety variables.

15.1.1.16 Modification 16: Improved instructions for collection of used sanitary products

Rationale: To provide more guidance to the investigators and site personnel.

List of protocol sections affected by this modification:

- Section 9.1 Tabular schedule of evaluations.

15.1.1.17 Modification 17: Correction of the in cervical smear instructions at EOT visit

Rationale: Mistake in the original protocol.

List of protocol sections affected by this modification:

- Section 9.2.9 36-month visit, EOT – Visit 8 (End of Year 8 of Mirena use)

15.1.1.18 Modification 18: Change in the SOPs to be followed for assessing important deviations

Rationale: CRO's SOPs will be used for the assessment of protocol deviations

List of protocol sections affected by this modification:

- Section 10.2 Analysis sets

15.1.1.19 Modification 19: Definition of a bleeding/spotting episode

Rationale: Correction of the bleeding intensity codes for bleeding/spotting episode

List of protocol sections affected by this modification:

- Section 9.6.3.12 Uterine bleeding
- Section 10.3.2.3.2 Bleeding pattern

15.1.1.20 Modification 20: Update of the background information

Rationale: To include recently published data about extended use of Mirena.

List of protocol sections affected by this modification:

- Section 3. Introduction
- Section 14 Reference list

15.1.1.21 Modification 21: Information on post-study contraception

Rationale: To inform the subject about the options for contraception after the study in order to decrease the chances for unplanned pregnancies after the study.

List of protocol section affected by this modification:

- Section 9.2.8 30-month visit – Visit 7

15.1.1.22 Modification 22: Mandatory TVUS if removal threads are not found

Rationale: To ensure that Mirena is in the appropriate intrauterine location and to exclude expulsion or perforation.

List of protocol section affected by this modification:

- Section 9.6.3.8 Presence of Mirena removal threads

15.1.1.23 Modification 23: Clarifications

Rationale: Textual editing for clarity and consistency between sections, administrative changes and corrections of mistakes.

List of protocol sections affected by this modification:

- Section 2. Synopsis
- Section 9.2 Visit description
- Section 11.1 Data recording
- Section 13.1 Investigators and other study personnel.

15.1.1.24 Modification 24: Instructions regarding bleeding irregularities detected in women using Mirena for contraception only

Rationale: As per FDA request

List of protocol sections affected by this modification:

- Section 9.1 Tabular schedule of evaluations
- Section 9.2 Visit description

15.1.1.25 Modification 25: Collection of age at Baseline visit (Visit 2)

Rationale: Age at baseline will be needed for the statistical analysis. As baseline might be up to 6 months after screening, the age at screening should not be used as it may not reflect the age at baseline.

List of protocol sections affected by this modification:

- Section 9.1 Tabular schedule of evaluations
- Section 9.2.3 Baseline – Visit 2
- Section 9.3.1 Demographic

- Section 10.2 Analysis sets
- Section 9.2 Visit description

15.1.1.26 Modification 26: Revision of the definition for start of treatment period for the primary variable

A new term 'extension treatment period' is introduced. This period starts at Day 1 of Year 6 of Mirena. Variables collected on an ongoing basis will primarily be analyzed for the 'extension treatment period' starting at Day 1 of Year 6 of Mirena use, i.e., data collected between the baseline visit and Day 1 of Year 6 of Mirena use will be excluded.

Rationale: This enables the calculation of the Pearl Index for the period of extended use of Mirena beyond the five years. Change was requested by the FDA.

List of protocol sections affected by this modification:

- Section 10.3 Variables and planned statistical analyses
- Section 10.3.1.1.1 Primary efficacy variable
- Section 10.3.1.2 Safety variables
- Section 10.3.2.1 Analysis of the primary variable
- Section 10.3.2.3 Analysis of safety variables
- Section 10.3.2.3.2 Bleeding pattern

15.1.2 Changes to the protocol text

In the sections on changes to the protocol text, all protocol sections affected by the respective amendment are detailed; the sequence of the sections follows the structure of the original protocol. As applicable, changes to the protocol text are highlighted as follows:

1. **Addition of a whole new portion**	Brief identification of the new portion
2. **Removal of a whole portion**	Complete display of the removed portion, formatted as ~~crossed out~~
3. **Editing of an existing portion**	Comparative presentation of "old text" versus "new text", with "old text" referring to the most recent previous protocol version. Deletions are ~~crossed out~~ in the "old text". Additions are <u>underlined</u> in the "new text".
• **Tables / figures**	The term "amended" is added to the caption.

• **Terminological changes**	Brief specification of the terminological change Thus, in this section, a terminological change (e.g. "period" versus "epoch") is defined only once, without displaying "old text" versus "new text" for each appearance.

Correction of typos or omissions are not highlighted in this section.

15.1.2.1 Section 2. Synopsis

This section was changed as a result of Modification 15.1.1.23

Old text:

Short title	Mirena ~~Extension study~~

New text:

Short title	Mirena Extended Trial

15.1.2.2 Section 3. Introduction

This section was changed as a result of Modification 15.1.1.20.

Old text:

[…]

~~Two controlled~~ contraceptive efficacy studies on extended use beyond the indicated 5 years up to 7 years (1, 2) have been published. In the recently published study by Rowe et al 2016, the overall pregnancy rate of the TCu380A was significantly higher than that of the LNG IUD: at the end of the seventh year the cumulative rate was 2.45 (standard error [SE] 0.44) per 100 for the TCu380A and 0.53 (SE 0.21) per 100 for the LNG IUD.

[…]

New text:

[…]

Three contraceptive efficacy studies on extended use beyond the indicated 5 years up to 7 years (1, 2, 3) have been published. In a comparative study the effectiveness of the contraceptive implant and the 52-mg hormonal intrauterine device in women using the method for 2 years beyond the approved duration was evaluated (1). Among 496 LNG IUS users, 696.9 woman-years of follow-up have been completed. Two pregnancies have been reported. The failure rate in the sixth year of use of the LNG IUS is calculated as 0.25 (95% CI, 0.04-1.42) per 100 woman-years; failure rate during the seventh year is 0.43 (95% CI 0.08-2.39) per 100 woman-years. In the recently published study by Rowe et al 2016 (2),

the overall pregnancy rate of the TCu380A was significantly higher than that of the LNG IUD: at the end of the seventh year the cumulative rate was 2.45 (standard error [SE] 0.44) per 100 for the TCu380A and 0.53 (SE 0.21) per 100 for the LNG IUD.

[…]

15.1.2.3 Section 5 Study design

This section was changed as a result of Modification 15.1.1.1.

Old text:

[…]

An analysis of the efficacy and safety data will be conducted after all subjects have either completed ~~7~~ years of treatment, or prematurely terminated their study participation before this time point.

[…]

New text:

[…]

An analysis of the efficacy and safety data will be conducted after all subjects have either completed 6 years of treatment (i.e. completed 1 year in the study), or prematurely terminated their study participation before this time point. Another analysis of the efficacy and safety data will be conducted after all subjects have either completed 7 years of treatment (i.e. completed 2 years in the study), or prematurely terminated their study participation before this time point.

[…]

15.1.2.4 Section 6 Study population

This section was changed as a result of Modification 15.1.1.2.

New text – addition of footnote 1:

[…]

The study will include fertile age women (18 to 35 years at the time of the screening visit) currently using a Mirena for contraception or for contraception and heavy menstrual bleeding and who have had the Mirena in situ for at least 4 years and 6 months but no longer than 5 years and are willing to continue its use for contraception or contraception and heavy menstrual bleeding for up to 8 years in total. About 90% of the women included will be 18 to 32 (inclusive) years of age at screening (visit 1)[1].

Text for Footnote 1: Screening of women who are 34 or 35 years old will be closed, once 10 women in this age group have completed the baseline visit, for details see Section 10.4.

15.1.2.5 Section 6.2 Exclusion criteria

This section was changed as a result of Modification 15.1.1.3 and 15.1.1.12.

Old text:

[…]

21. Laboratory values outside inclusion range before baseline and considered clinically relevant.
22. Simultaneous participation in another clinical ~~trial~~. Participation in another clinical trial prior to study entry that might have an impact on the study objectives, at the discretion of the investigator.

New text:

[…]

21. Laboratory values outside inclusion range before baseline and considered clinically relevant (see Section 9.6.3.7).
22. Simultaneous participation in another clinical study with investigational medicinal product(s). Participation in another clinical trial prior to study entry that might have an impact on the study objectives, at the discretion of the investigator.

[…]

15.1.2.6 Section 6.4.1 Withdrawal

This section was changed as a result of Modification 15.1.1.4 and 15.1.1.13.

Old text:

[…]

Subjects *must* be withdrawn from the study if any of the following occurs:

- […]
- Acute pelvic inflammatory disease (PID) not responding to treatment
- Genital malignancy
- Liver tumor (benign or malignant)
- Allergic reaction to the study medication or any of its components
- If, in the investigator's opinion, continuation of the study would be harmful to the subject's well-being
- […]

Subjects *may* be withdrawn from the study if any of the following occurs:

- […]
- Marked increase of blood pressure
- ~~Severe arterial disease such as stroke or myocardial infarction~~
- ~~Uterine or cervical malignancy~~
- Jaundice
- […]
- ~~Should the subject, during the course of the study, develop conditions which would have prevented her entry into the study according to the exclusion criteria, she must be withdrawn immediately if safety is concerned. In other cases, the investigator will decide if there is a conflict with study objectives.~~
- At the specific request of the sponsor and in liaison with the investigator (e.g. obvious non-compliance, safety concerns).

The reasons for any withdrawal are to be fully documented on the eCRF.

[…]

New text:

[…]

Subjects *must* be withdrawn from the study if any of the following occurs:

- […]
- Acute pelvic inflammatory disease (PID) not responding to treatment
- Genital malignancy (e.g., uterine or cervical malignancy)
- Severe arterial disease such as stroke or myocardial infarction
- Liver tumor (benign or malignant)
- Allergic reaction to the study medication or any of its components
- If, in the investigator's opinion, continuation of the study would be harmful to the subject's well-being
- Should the subject, during the course of the study, develop conditions which would have prevented her entry into the study according to the exclusion criteria, she must be withdrawn immediately if safety is concerned. In other cases, the investigator will decide if there is a conflict with study objectives.
- […]

Subjects *may* be withdrawn from the study if any of the following occurs:

- […]
- Marked increase of blood pressure
- Jaundice
- […]
- At the specific request of the sponsor and in liaison with the investigator (e.g. obvious non-compliance, safety concerns).
- Return of heavy menstrual bleeding, if it affects the subject's well-being, based on the investigator's clinical judgment

The reasons for any withdrawal are to be fully documented on the eCRF.

[…]

15.1.2.7 Section 9.1 Tabular schedule of evaluations

This section was changed as a result of Modification 15.1.1.1, 15.1.1.16, 15.1.1.24, and 15.1.1.25.

Old text:

Table 9–1 Schedule of activities and evaluations

Period	Screening (0 to 6 mo)			Treatment Period (3 years; Mirena years 6 thru 8)						Pregnancy Follow-up (up to 12 mo)		
Visit	Prescreening contact (optional)	Screening	Baseline						EOT[a]	EOS All subjects	3-mo contact [b]	12-mo contact [c]
Visit number	☎/✉	1	2	3	4	5	6	7	8	☎	☎	☎
Timing		within 60 days	Day 1	6 mo ±14 d	12 mo ±14 d	18 mo ±14 d	24 mo ±14 d	30 mo ±14 d	36 mo -14 d	3 wks after EOT -3 d	3 mo after EOT -7 d/+14 d	12 mo after EOT +7 d
Duration of Mirena use		4 y 6 mo to 5 years	5 years[d]		6 years		7 years		8 years			
[…]												
Demography		X										
[…]												
Physical examination		X					X		X			
Vital signs, body weight		X+height					X		X			
Gynecological exam. incl. breast palpation		X					X		X			
[…]												
Urine pregnancy test [g]		X	X	X	X	X	X	X	X	X		
[…]												
Dispense home pregnancy test kits			X	X	X	X	X	X				
[…]												
Subject satisfaction with Mirena			X				X		X			

Footnote explanations:

c ~~For~~ subjects that prematurely discontinued treatment due to 'Wish for pregnancy' will be contacted. If a subject was not pregnant at 3 month contact and no longer wished to become pregnant, a 12-month contact is not required. If a subject was "Lost to Follow-up" at 3 month contact, a 12-month contact is required. See also Section 9.4.1.

[…]

g In addition to the urine pregnancy tests performed by the site at each study visit, subjects will be given home urine pregnancy tests to be used whenever a

pregnancy is suspected. Subjects must contact the study site immediately if a pregnancy test is positive. Home pregnancy test is to be done on the day of the 3-week contact.

New text:

Table 9–1 Schedule of activities and evaluations – amended

Period	**Screening (0 to 6 mo)**			**Treatment Period (3 years; Mirena years 6 thru 8)**						**Pregnancy Follow-up (up to 12 mo)**		
Visit	**Prescreening contact (optional)**	**Screening**	**Baseline**						**EOT[a]**	**EOS All subjects**	**3-mo contact [b]**	**12-mo contact [c]**
Visit number	☎/✉	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	☎	☎	☎
Timing		**within 60 days**	**Day 1**	**6 mo ±14 d**	**12 mo ±14 d**	**18 mo ±14 d**	**24 mo ±14 d**	**30 mo ±14 d**	**36 mo -14 d**	**3 wks after EOT -3 d**	**3 mo after EOT -7 d/+14 d**	**12 mo after EOT +7 d**
Duration of Mirena use		**4 y 6 mo to 5 years**	**5 years[d]**		**6 years**		**7 years**		**8 years**			
[…]												
Demography		X										
Age at baseline			X									
[…]												
Physical examination		X			X		X		X			
Vital signs, body weight		X+height			X		X		X			
Gynecological exam. incl. breast palpation		X			X		X		X			
[…]												
Urine pregnancy test [g]		X	X	X	X	X	X	X	X	X [g]		
[…]												
Dispense home pregnancy test kits			X	X	X	X	X	X	X			
[…]												
Subject satisfaction with Mirena			X		X		X		X			
[…]												

Footnote explanations:

c Subjects that prematurely discontinued treatment due to ‘Wish for pregnancy’ will be contacted. If a subject was not pregnant at 3 month contact and no

longer wished to become pregnant, a 12-month contact is not required. If a subject was “Lost to Follow-up” at 3 month contact, a 12-month contact is required. See also Section 9.4.1.

[…]

g In addition to the urine pregnancy tests performed by the site at each study visit, subjects will be given home urine pregnancy tests to be used whenever a pregnancy is suspected. Subjects must contact the study site immediately if a pregnancy test is positive. Home pregnancy test is to be done on the day of the 3-week contact.

[…]
d=day, EOS=end of study, EOT=end of treatment, mo=month, PK=pharmacokinetics, wks=weeks, y=year

Old text:

[…]

Subjects in the HMB subgroup (i.e. all women who had the Mirena inserted for contraception and heavy menstrual bleeding) will collect their used sanitary products (provided by sponsor) during 4 periods of 30 days as shown in Table 9-2. All used sanitary products have to be returned to the study site ~~at time points given~~ in Table 9-2.

[…]

New text:

[…]

Subjects in the HMB subgroup (i.e. all women who had the Mirena inserted for contraception and heavy menstrual bleeding) will collect their used sanitary products (provided by sponsor) during 4 periods of 30 days as shown in Table 9-2. All used sanitary products have to be returned to the study site as instructed in Section 9.4.2 and displayed in Table 9-2.

[…]

Old text:

[…]

Table 9–2 Schedule of activities needed for the MBL evaluations

HMB subgroup only – additional activities for baseline (BL) visit and treatment period

Period	**Screening**	**Treatment Period (Mirena years 6 thru 8)**										
		30 days after baseline visit			**~~30 days prior to~~ visit 4**			**~~30 days prior to~~ visit 6**			**~~30 days prior to~~ EOT**	
Visit / visit number	**Baseline (BL) Visit 2**	**Return**	**Return**	**Visit 3**	**Return**	**Visit 4**	**Visit 5**	**Return**	**Visit 6**	**Visit 7**	**Return**	**EOT Visit 8**
~~Timing~~	~~2 weeks~~	~~2 weeks after BL~~	~~30 days after BL~~	~~6 mo ±2 weeks~~	~~2 weeks before V4~~	~~12 mo ±2 weeks~~	~~18 mo ±2 weeks~~	~~2 weeks before V6~~	~~24 mo ±2 weeks~~	~~30 mo ±2 weeks~~	~~2 weeks before EOT~~	~~36 mo 2 weeks~~
Dispense alkaline hematin kit	X			X			X			X		
Collection of used ~~towels and tampons~~		→	→		→	→		→	→		→	→
Return of used ~~towels and tampons~~		X	X		X	X		X	X		X	X

~~Note:~~ Return required only if sanitary ~~protection has~~ been used in the time periods indicated.
~~Note: For all other activities and evaluations, please refer to Table 9-1.~~

New text:

[…]

For subjects who have the Mirena inserted for contraception only: if bleeding irregularities develop during prolonged treatment, appropriate diagnostic measures should be taken by the investigator to rule out endometrial pathology.

Table 9–2 Schedule of activities needed for the MBL evaluations – amended

HMB subgroup only – additional activities for baseline (BL) visit and treatment period. For all other activities and evaluations, see Table 9-1.

Period	**Screening**	**Treatment Period (Mirena years 6 thru 8)**										
Collection time		**30 days after baseline visit, Study Days 2 to 31 (inclusive)**			**Study Days 322 to 351 (inclusive) before Visit 4**			**Study Days 687 to 716 (inclusive) before Visit 6**			**Study Days 1052 to 1081 (inclusive) before EOT visit**	
Visit / visit number	**Baseline (BL) Visit 2**	**Return**	**Return**	**Visit 3**	**Return**	**Visit 4**	**Visit 5**	**Return**	**Visit 6**	**Visit 7**	**Return**	**EOT Visit 8**
Dispense alkaline hematin kit	X			X			X			X		
Collection of used sanitary products		→	→		→	→		→	→		→	→
Return of used sanitary products[a]		X	X		X	X		X	X		X	X

Study Day 1 = Day of the baseline visit (Visit 2)
a Used sanitary products should not be kept at home longer than 14 days. Return required only if sanitary products have been used in the time periods indicated.

15.1.2.8 Section 9.2 Visit description

This section was changed as a result of Modification 15.1.1.23.

Old text:

The timing of the visits is based on the date of the baseline visit. Treatment period starts at the baseline visit (Visit 2, defined as Day 1).

New text:

The timing of the visits is based on the date of the baseline visit. Treatment period starts at the baseline visit (Visit 2, defined as Study Day 1).

15.1.2.9 Section 9.2.3 Baseline – Visit 2

This section was changed as a result of Modification 15.1.1.25.

Old text:

The following procedures and assessments will be done:

- Re-check inclusion/exclusion criteria (Sections 6.1 and 6.2)
- Perform pelvic examination to visualize Mirena removal threads (Section 9.6.3.8)
- […]

New text:

The following procedures and assessments will be done:

- Re-check inclusion/exclusion criteria (Sections 6.1 and 6.2)
- Age at baseline (Section 9.3.1)
- Perform pelvic examination to visualize Mirena removal threads (Section 9.6.3.8)
- […]

15.1.2.10 Section 9.2.5 12-month visit – Visit 4 (End of Year 6 of Mirena use)

This section was changed as a result of Modification 15.1.1.1.

Old text:

The following procedures and assessments will be done:

- Perform pelvic examination to visualize Mirena removal threads (Section 9.6.3.8)
- Perform urine pregnancy test (Section 9.6.3.4)
- Perform safety laboratory test and urinalysis (Section 9.6.3.7)
- Blood sample for PK (Note: **subjects randomized to this visit**) (Section 9.5.1)
- Interview for the following:
    - Concomitant medications (Section 8.1)
    - AEs (Section 9.6.1)
    - Continuing need for contraception (Section 9.7.1)
- Dispense home pregnancy kits with instructions (Section 9.6.3.4)
- Review completed (monthly) eDiary, including information on uterine bleeding and back-up contraception.

New text:

The following procedures and assessments will be done:

- Assess vital signs and weight (Section 9.6.3.1)
- Perform general physical examination (Section 9.6.3.2)
- Perform gynecological examination (with **breast palpation**; Section 9.6.3.3
- Perform pelvic examination to visualize Mirena removal threads (Section 9.6.3.8)
- Perform urine pregnancy test (Section 9.6.3.4)
- Perform safety laboratory test and urinalysis (Section 9.6.3.7)
- Blood sample for PK (Note: **subjects randomized to this visit**) (Section 9.5.1)
- Interview for the following:
    - Concomitant medications (Section 8.1)
    - AEs (Section 9.6.1)
    - Continuing need for contraception (Section 9.7.1)
- Dispense home pregnancy kits with instructions (Section 9.6.3.4)
- Review completed (monthly) eDiary, including information on uterine bleeding and back-up contraception.
- Subject satisfaction with Mirena (Section 9.7.4).

15.1.2.11 Section 9.2.8 30-month visit – Visit 7

This section was changed as a result of Modification 15.1.1.21.

Old text:

[…]

- Dispense alkaline hematin kit with instructions for subjects in HMB group.

New text:

[…]

- Dispense alkaline hematin kit with instructions for subjects in HMB group.

Discuss the contraceptive options available after the study treatment with the subject (see Section 8.2).

15.1.2.12 Section 9.2.9 36-month visit, EOT – Visit 8 (End of Year 8 of Mirena use)

This section was changed as a result of Modification 15.1.1.17.

Old text:

The following procedures and assessments will be done:

[…]

- Perform pelvic examination to visualize Mirena removal threads (Section 9.6.3.8)
- Obtain cervical smear (Section 9.6.3.5). ~~A cervical smear should be taken at this visit or a documented normal result (using the Bethesda system or a corresponding system) has to have been obtained within 6 months before the Screening Visit (Visit 1). Subjects with ASCUS can be included if they have a HPV DNA test that, according to the standards of the local laboratory, is negative for high risk HPV. A cervical smear may be repeated once if the screening result is abnormal.~~
- Perform urine pregnancy test (Section 9.6.3.4)
- Perform safety laboratory test and urinalysis (Section 9.6.3.7)
- Blood sample for PK (**all subjects**) (Section 9.5.1)
- Interview for the following:
    - Concomitant medications (Section 8.1)
    - AEs (Section 9.6.1)
    - Continuing need for contraception (Section 9.7.1)
- Review completed (monthly) eDiary, including information on uterine bleeding and back-up contraception.
- Collect eDiary device (Section 9.7.1)
- Subject satisfaction with Mirena (Section 9.7.4)
- Remove the Mirena (Section 9.7.3)
    - Complete Mirena removal ease (investigator) and pain (subject) assessment

New text:

The following procedures and assessments will be done:

- Assess vital signs and weight (Section 9.6.3.1)
- Perform general physical examination (Section 9.6.3.2)
- Perform gynecological examination (with **breast palpation**; Section 9.6.3.3)
- Perform pelvic examination to visualize Mirena removal threads (Section 9.6.3.8)
- Obtain cervical smear (Section 9.6.3.5)
- Perform urine pregnancy test (Section 9.6.3.4)

- Perform safety laboratory test and urinalysis (Section 9.6.3.7)
- Blood sample for PK (**all subjects**) (Section 9.5.1)
- Interview for the following:
    - Concomitant medications (Section 8.1)
    - AEs (Section 9.6.1)
    - Continuing need for contraception (Section 9.7.1)
- Dispense home pregnancy kits with instructions (Section 9.6.3.4)
- Review completed (monthly) eDiary, including information on uterine bleeding and back-up contraception.

15.1.2.13 Section 9.2.10 3-week follow-up call (EOS)

This section was changed as a result of Modification 15.1.1.6.

Old text:

All subjects will be contacted 3 weeks after EOT (i.e. after Mirena removal) to collect information on any pregnancy detected shortly after the end of study treatment.

New text:

All subjects will be contacted 3 weeks after EOT (i.e. after Mirena removal) to collect information on any pregnancy detected shortly after the end of study treatment, see Section 9.4.1.

15.1.2.14 Section 9.2.11 3-month follow-up contact for post-study pregnancies

This section was changed as a result of Modification 15.1.1.6.

Old text:

Subjects who prematurely discontinued study treatment will be contacted by phone unless the reason for discontinuation is “pregnancy”, “death”, or “withdrawal by subject” where the subject has withdrawn main consent during study conduct and wishes to stop future contact with the site. For subjects that had withdrawn consent during study, but consented to post study participation follow-up, post treatment pregnancy tracking information is expected. At this time, subjects will be asked if they have been pregnant after the study (i.e. after the 3-week follow-up call). Please see Section 9.4.1.

New text:

Subjects who prematurely discontinued study treatment will be contacted by phone unless the reason for discontinuation is “pregnancy”, “death”, or “withdrawal by subject” where the subject has withdrawn main consent during study conduct and wishes to stop future contact

with the site. For subjects that had withdrawn consent during study, but consented to post study participation follow-up, post treatment pregnancy tracking information is expected. At this time, subjects will be asked if they have been pregnant after the study (i.e. after the 3-week follow-up call). This contact is part of the Post-Treatment Pregnancy Tracking (PTPT) process, see Section 9.4.1.

15.1.2.15 Section 9.2.12 12-months follow-up contact for return-to-fertility

This section was changed as a result of Modification 15.1.1.6.

Old text:

Subjects that prematurely discontinued treatment due to 'Wish for pregnancy' will be contacted and asked about pregnancies that occurred within 12 months after end of treatment (EOT, i.e. removal of Mirena). If a subject was not pregnant at 3 month contact and no longer wished to become pregnant, a 12-month contact is not required. If subject was "Lost to Follow-up" at 3 months, a 12-month contact is required~~. Please~~ see Section 9.4.1.

New text:

Subjects that prematurely discontinued treatment due to 'Wish for pregnancy' will be contacted and asked about pregnancies that occurred within 12 months after end of treatment (EOT, i.e. removal of Mirena). If a subject was not pregnant at 3 month contact and no longer wished to become pregnant, a 12-month contact is not required. If subject was "Lost to Follow-up" at 3 months, a 12-month contact is required. This contact is part of the Post-Treatment Pregnancy Tracking (PTPT) process, see Section 9.4.1.

15.1.2.16 Section 9.3.1 Demographic

This section was changed as a result of Modification 15.1.1.25.

Old text:

Demographic data [e.g. year of birth, age at the screening (Visit 1), race, ethnic group, educational level] and other population characteristics including tobacco use and alcohol consumption will be collected at time points presented in Table 9-1.

New text:

Demographic data [e.g. year of birth, age at the screening (Visit 1), age at baseline (Visit 2), race, ethnic group, educational level] and other population characteristics including tobacco use and alcohol consumption will be collected at time points presented in Table 9-1.

15.1.2.17 Section 9.4.1.1 Pregnancies during the study

This section was changed as a result of Modification 15.1.1.6.

Old text:

The investigator must report to the sponsor any pregnancy occurring in a study subject during her participation in this study~~.~~ This report is to be submitted within the same timeframe as an SAE (i.e. no later than 24 hours of having gained knowledge of the event), although a pregnancy, per se, is not considered an AE/SAE.

New text:

The investigator must report to the sponsor any pregnancy occurring in a study subject during her participation in this study <u>including pregnancies detected at the contact 3 weeks after EOT.</u> This report is to be submitted within the same timeframe as an SAE (i.e. no later than 24 hours of having gained knowledge of the event), although a pregnancy, per se, is not considered an AE/SAE.

15.1.2.18 Section 9.4.1.2 Pregnancies occurring after the end of study treatment

This section was changed as a result of Modification 15.1.1.5 and 15.1.1.6.

Old text:

All pregnancies detected up to 3 months after the removal of the Mirena must be reported to the sponsor; all subjects will be instructed to contact the investigator immediately if they become pregnant less than 3 months after the removal of the Mirena. If the estimated date of conception is suspected to have occurred during study treatment, further investigations will be conducted, and the pregnancy should be reported immediately and will be followed up according to the process described above for pregnancies during the study.

~~**3 weeks after EOT:** All subjects will be contacted 3 weeks after EOT to collect information on any pregnancy detected shortly after the end of study treatment.~~

New text:

All pregnancies detected up to 3 months after the removal of the Mirena must be reported to the sponsor; all subjects will be instructed to contact the investigator immediately if they become pregnant less than 3 months after the removal of the Mirena. If the estimated date of conception is suspected to have occurred during study treatment <u>(i.e. up to 7 days after EOT)</u>, further investigations will be conducted, and the pregnancy should be reported immediately and will be followed up according to the process described above for pregnancies during the study.

[…]

Old text:

~~Post-study pregnancy tracking information,~~ including information on all pregnancies identified, must be reported to the sponsor via electronic data collection tool (see Section 11.1). In addition, if the estimated date of conception is suspected to have occurred during study treatment, the pregnancy should be reported immediately according to the process described under section 9.4.1.1.

New text:

PTPT information, i.e. data collected at the 3- and 12-month follow-up contacts, including information on all pregnancies identified, must be reported to the sponsor via electronic data collection tool (see Section 11.1). In addition, if the estimated date of conception is suspected to have occurred during study treatment, the pregnancy should be reported immediately according to the process described under section 9.4.1.1.

[…]

15.1.2.19 Section 9.6.3.6 Test for chlamydia

This section was changed as a result of Modification 15.1.1.14.

Old text:

[…]

A single repeat test is permissible if the screening results are positive. If the test result is positive, the subject must also be tested for gonorrhea. Gonorrhea tests must also be performed using a highly accurate test method ~~in a local laboratory~~ that meets the standards of GLP. A subject with an active genital infection may not be assigned to study treatment until the infection has been successfully treated (see Section 6.2, Exclusion criterion 4).

[…]

New text:

[…]

A single repeat test is permissible if the screening results are positive. If the test result is positive, the subject must also be tested for gonorrhea. Gonorrhea tests must also be performed using a highly accurate test method that meets the standards of GLP. A subject with an active genital infection may not be assigned to study treatment until the infection has been successfully treated (see Section 6.2, Exclusion criterion 4).

[…]

15.1.2.20 Section 9.6.3.7 Safety laboratory tests

This section was changed as a result of Modification 15.1.1.3.

Old text:

Only blood samples analyzed at the central laboratory will be considered for analysis. The name and address for the central lab service provider can be found in the documentation supplied by the vendor. The safety laboratory tests may be repeated once during the screening period if laboratory values are outside the inclusion range and assessed as clinically relevant.

New text:

Only blood samples analyzed at the central laboratory will be considered for analysis. The name and address for the central lab service provider can be found in the documentation supplied by the vendor. For a given laboratory parameter, the acceptable values for inclusion would consist of values within the reference ranges, measured at baseline, as provided in the Covance Central Laboratory Services (CCLS) Manual for Bayer Protocol 18649 (Covance Project #: 518179). The safety laboratory tests may be repeated once during the screening period if laboratory values are outside the inclusion range and assessed as clinically relevant.

15.1.2.21 Section 9.6.3.8 Presence of Mirena removal threads

This section was changed as a result of Modification 15.1.1.22.

Old text:

[…]

The investigator will perform pelvic examinations at each study visit to verify the presence of the Mirena removal threads in the appropriate location in the cervical os. ~~At the investigator's discretion,~~transvaginal ultrasound (TVUS)~~ may be~~ performed to verify that the Mirena is in the appropriate intrauterine location and to exclude expulsion or perforation. […]

New text:

[…]

The investigator will perform pelvic examinations at each study visit to verify the presence of the Mirena removal threads in the appropriate location in the cervical os. If the presence of the removal threads cannot be verified, transvaginal ultrasound (TVUS) is to be performed to verify that the Mirena is in the appropriate intrauterine location and to exclude expulsion or perforation. […]

15.1.2.22 Section 9.6.3.12 Uterine bleeding

This section was changed as a result of Modification 15.1.1.19.

Old text

Table 9-3 Uterine bleeding – bleeding intensity definitions

Category	Intensity	Definition
None	None	No uterine bleeding
Spotting	Spotting	Less than associated with normal menstruation relative to the woman's experience, with no need for sanitary protection except for panty liners
Bleeding	Light	Less than associated with normal menstruation relative to the woman's experience, with need for sanitary protection
	Normal	Like normal menstruation relative to the woman's experience
	Heavy	More than normal menstruation relative to the woman's experience

New text:

Table 9-3 Uterine bleeding – bleeding intensity definitions

Category	Intensity	Bleeding Intensity Code	Definition
None	None	1	No uterine bleeding
Spotting	Spotting	2	Less than associated with normal menstruation relative to the woman's experience, with no need for sanitary protection except for panty liners
Bleeding	Light	3	Less than associated with normal menstruation relative to the woman's experience, with need for sanitary protection
	Normal	4	Like normal menstruation relative to the woman's experience
	Heavy	5	More than normal menstruation relative to the woman's experience

15.1.2.23 Section 9.7.1 eDiary

This section was changed as a result of Modification 15.1.1.23.

Old text:

[…]

The use of the eDiary will be explained in detail in a site manual, and the site personnel will train the subject on how to use the device at the baseline visit. At all the following visits (see Table 9-1), the eDiary entries will be checked and documented by the study site personnel for completeness. […]

New text:

[…]

Subject will enter her data daily into the eDiary. The use of the eDiary will be explained in detail in a site manual, and the site personnel will train the subject on how to use the device at the baseline visit. At all the following visits (see Table 9-1), the eDiary entries will be checked and documented by the study site personnel for completeness. […]

15.1.2.24 Section 9.7.4 Subject satisfaction with Mirena

This section was changed as a result of Modification 15.1.1.1.

Old text:

At baseline visit, visit 6 and at the end of the treatment (EOT, visit 8) (see also Table 9-1), the subject is asked to evaluate her satisfaction with the Mirena on a 5-point scale as very satisfied, somewhat satisfied, neither satisfied or dissatisfied, dissatisfied or very dissatisfied. Information regarding the subject satisfaction will be documented by the investigator in eCRF.

New text:

At baseline visit, visit 4, 6 and at the end of the treatment (EOT, visit 8) (see also Table 9-1), the subject is asked to evaluate her satisfaction with the Mirena on a 5-point scale as very satisfied, somewhat satisfied, neither satisfied or dissatisfied, dissatisfied or very dissatisfied. Information regarding the subject satisfaction will be documented by the investigator in eCRF.

15.1.2.25 Section 10.2 Analysis sets

This section was changed as a result of Modification 15.1.1.1, 15.1.1.18 and 15.1.1.25.

Old text:

The documentation of important deviations and the assignment of subjects to analysis sets will be performed according to the ~~sponsor's~~ applicable Standard Operating Procedures and/or Instruction Manuals.

The following statistical analysis sets will be defined:

Full analysis set (FAS):
All women who completed the baseline visit of the study

Primary analysis set Year 7 (PAS year 7):
All women in the FAS with an age of 34 years or younger at baseline visit (i.e., an age of 36 or younger at end of year 7)

Primary analysis set Year 8 (PAS year 8):
All women in the FAS with an age of 33 years or younger at baseline visit (i.e., an age of 36 or younger at end of year 8)

***Safety analysis set (SAF)*:**
All women who completed the baseline visit of the study, analyzed for the FAS

The age at baseline (required for PAS year 7 and PAS year 8) will be ~~approximated as the difference between year of baseline visit and year of birth recorded at screening visit.~~

New text:

The documentation of important deviations and the assignment of subjects to analysis sets will be performed according to the CRO´s applicable Standard Operating Procedures and/or Instruction Manuals.

The following statistical analysis sets will be defined:

Full analysis set (FAS):
All women who completed the baseline visit of the study

Primary analysis set Year 6 (PAS year 6):
All women in the FAS with an age of 35 years or younger at baseline visit (i.e., an age of 36 or younger at end of year 6)

Primary analysis set Year 7 (PAS year 7):
All women in the FAS with an age of 34 years or younger at baseline visit (i.e., an age of 36 or younger at end of year 7)

Primary analysis set Year 8 (PAS year 8):
All women in the FAS with an age of 33 years or younger at baseline visit (i.e., an age of 36 or younger at end of year 8)

***Safety analysis set (SAF)*:**
All women who completed the baseline visit of the study, analyzed for the FAS

The age at baseline (required for PAS year 6, PAS year 7 and PAS year 8) will be used as recorded at the baseline visit 2.

15.1.2.26 Section 10.3 Variables and planned statistical analyses

This section was changed as a result of Modification 15.1.1.26.

New text added (no old text):

In order to allow some flexibility, the baseline visit is planned to take place 14 to 0 days before the end of Year 5 of Mirena use (see Table 9-1). As a consequence, it is expected there will be various subjects with that baseline visit taking place prior to the start of 'extension treatment period', i.e. Day 1 of Year 6 of Mirena use.

Variables collected on an ongoing basis will primarily be analyzed for the 'extension treatment period' starting at Day 1 of Year 6 of Mirena use, i.e., data collected between the baseline visit and Day 1 of Year 6 of Mirena use will be excluded:

- Primary efficacy variable, i.e. occurrence of pregnancies (section 10.3.2.1)

- Main safety variable, i.e. adverse events (section 10.3.2.3.1)
- Uterine bleeding / bleeding pattern (section 10.3.2.3.2)

Variables collected at pre-specified visits/timeframes only will be analyzed per visit (unless otherwise stated):

- Secondary efficacy variable, i.e. menstrual blood loss (section 10.3.2.2)
- Other safety variables, not listed above (section 10.3.2.3)
- Other variables (section 10.3.2.4)

More details will be provided in the statistical analysis plan.

15.1.2.27 Section 10.3.1.1.1 Primary efficacy variable

This section was changed as a result of Modifications 15.1.1.1 and 15.1.1.26.

Old text:

The primary efficacy variable is the occurrence of pregnancy within years 6 thru 8 of Mirena use. However, for the analysis after 7 years, the primary efficacy variable is the occurrence of pregnancy within years 6 thru 7 of Mirena use.

The PI is defined as the number of pregnancies per 100 woman years. The following PIs will be calculated:

- '~~Two~~ years PI (sixth & seventh year)', PI obtained in the sixth and seventh year of treatment, i.e., number of pregnancies that occurred during the sixth and seventh year of treatment divided by time the women were under risk of getting pregnant in the sixth and seventh year of treatment.
- '~~Three~~ years PI (sixth, seventh & eighth year)', PI obtained in the sixth, seventh and eighth year of treatment, i.e., number of pregnancies that occurred during the sixth, seventh and eighth year of treatment divided by time the women were under a risk of getting pregnant in the sixth, seventh and eighth year of treatment.
- 'Overall PI', PI obtained during the whole study, i.e., number of pregnancies that occurred during the ~~studied treatment~~ period ~~beyond 5 years~~ divided by the time the women were under a risk of getting pregnant.

New text:

The primary efficacy variable is the occurrence of pregnancy within years 6 thru 8 of Mirena use. However, for the analysis after 6 years of Mirena use, the primary efficacy variable is the occurrence of pregnancy within year 6 of Mirena use, and for the analysis after 7 years, the primary efficacy variable is the occurrence of pregnancy within years 6 thru 7 of Mirena use.

The PI is defined as the number of pregnancies per 100 woman years. The Pearl Index will be analyzed for the 'extension treatment period' starting at Day 1 of Year 6 of Mirena use, i.e.,

exposure and pregnancies between the baseline visit and Day 1 of Year 6 of Mirena use will be excluded. The following PIs will be calculated:

- '1-year PI' (sixth year)', PI obtained in the sixth year of treatment, i.e., number of pregnancies that occurred during the sixth year of treatment divided by time the women were under risk of getting pregnant in the sixth year of treatment.
- '2-year PI (sixth & seventh year)', PI obtained in the sixth and seventh year of treatment, i.e., number of pregnancies that occurred during the sixth and seventh year of treatment divided by time the women were under risk of getting pregnant in the sixth and seventh year of treatment.
- '3-year PI (sixth, seventh & eighth year)', PI obtained in the sixth, seventh and eighth year of treatment, i.e., number of pregnancies that occurred during the sixth, seventh and eighth year of treatment divided by time the women were under a risk of getting pregnant in the sixth, seventh and eighth year of treatment.

Furthermore, the following PI will be analyzed for the entire study period starting at baseline visit, i.e., exposure and pregnancies between the baseline visit and Day 1 of Year 6 of Mirena use will be included:

- 'Overall PI', PI obtained during the whole study, i.e., number of pregnancies that occurred during the entire study period starting at baseline visit divided by the time the women were under a risk of getting pregnant.

15.1.2.28 Section 10.3.1.2 Safety variables

This section was changed as a result of Modification 15.1.1.15 and 15.1.1.26.

Old text:

The main safety variable is the incidence of ~~post-baseline~~ adverse events (both serious and non-serious).

Other safety variables are:

- Uterine bleeding / Bleeding pattern
- Vital signs and weight
- ~~Physical examination~~
- ~~Gynecological examination~~

[…]

New text:

The main safety variable is the incidence of treatment-emergent adverse events (both serious and non-serious). Treatment-emergent AEs are defined as any AEs occurring during the 'extension treatment period' starting at Day 1 of Year 6 of Mirena use.

Other safety variables are:

- Uterine bleeding / Bleeding pattern
- Vital signs and weight

[…]

15.1.2.29 Section 10.3.2.1 Analysis of the primary variable

This section was changed as a result of Modification 15.1.1.1, 15.1.1.5, 15.1.1.7, 15.1.1.8, 15.1.1.9 and 15.1.1.26.

Old text:

The primary variable is the occurrence of pregnancy within years 6-8 of Mirena use. However, for the analysis after 7 years, the primary variable is the occurrence of pregnancy within years 6 thru 7 of Mirena use.

New text:

The primary variable is the occurrence of pregnancy within years 6-8 of Mirena use. However, for the analysis after 6 years, the primary variable is the occurrence of pregnancy within years 6 of Mirena use, and for the analysis after 7 years, the primary variable is the occurrence of pregnancy within years 6 thru 7 of Mirena use.

[…]

Old text:

Table 10–1 Definition of crude exposure times

PI	Reason for end of study/ continuation status	Crude exposure time
~~Two~~ years PI (sixth & seventh year)	Total expulsion	Date, when expulsion was ~~realized~~ ~~Baseline visit date~~ +1
	Partial Expulsion/ Mirena removal	Date of Mirena removal – ~~Baseline visit date~~ +1
	Pregnancy	Date of conception – ~~Baseline visit date~~ +1
	Lost to Follow up	~~Max~~ (Date Mirena last known in situ – ~~Baseline visit date~~ +1, ~~0~~)
	Continues into 8th year of treatment	730 days
~~Three~~ years PI (sixth, seventh & eighth year)	Total expulsion	Date, when expulsion was ~~realized~~ ~~Baseline visit date~~ +1
	Partial Expulsion/ Mirena removal	Date of Mirena removal – ~~Baseline visit date~~ +1
	Pregnancy	Date of conception – ~~Baseline visit date~~ +1
	Lost to Follow up	~~Max~~ (Date Mirena last known in situ – ~~Baseline visit date~~ +1, ~~0~~)

PI	Reason for end of study/ continuation status	Crude exposure time
	Continues into 9th year of treatment	~~Min~~ (1095 days, Date of EOT visit – ~~Baseline visit date~~ +1)
Overall PI	Total expulsion	Date, when expulsion was ~~realized~~ –Baseline visit date +1
	Partial Expulsion/ Mirena removal	Date of Mirena removal – Baseline visit date +1
	Pregnancy	Date of conception – Baseline visit date +1
	Lost to Follow up	~~Max~~ (Date Mirena last known in situ – Baseline visit date +1, ~~0~~)
	Continued until EOT	Date of EOT visit – Baseline visit date +1

A pregnancy will be allocated to the time period(s) that are relevant for the calculation of the PIs described above, e.g., a pregnancy that occurs on day 400 will be relevant for the 7th year PI, the two years PI (6th and 7th year), the three years PI (6th, 7th and 8th year), and the overall PI. Pregnancies that occur after the Mirena was removed or an expulsion was realized will not count for any PI.

[…]

Exposure times to be subtracted:

Subjects who apply additional concomitant contraception are not in risk or are under a lower risk of getting pregnant than subjects who do not apply additional contraception. In case a subject uses concomitant contraceptive methods (e.g., condoms to prevent STD) the period of additional contraceptive method use will be excluded from the exposure time.

[…]

The primary analysis set will be the PAS ~~y~~ear 7 (for the analysis after 7 years) and the PAS ~~y~~ear 8 (for the final analysis after 8 years), respectively. Furthermore, analyses will be repeated for the FAS.

New text:

Table 10–1 Definition of crude exposure times – amended

PI	Reason for end of study/ continuation status	Crude exposure time
1-year PI (6th year)	Total expulsion	Date, when expulsion was discovered – Date of Day 1 Year 6 +1
	Partial Expulsion/ Mirena removal	Date of Mirena removal – Date of Day 1 Year 6 +1
	Pregnancy	Date of conception – Date of Day 1 Year 6 +1
	Lost to Follow up	Maximum of (Date Mirena last known in situ – Date of Day 1 Year 6 +1; 1 day)
	Continues into 7th year of treatment	365 days
2-year PI (6th and 7th year)	Total expulsion	Date, when expulsion was discovered – Date of Day 1 Year 6 +1
	Partial Expulsion/ Mirena removal	Date of Mirena removal – Date of Day 1 Year 6 +1
	Pregnancy	Date of conception – Date of Day 1 Year 6 +1
	Lost to Follow up	Maximum of (Date Mirena last known in situ – Date of Day 1 Year 6 +1; 1 day)
	Continues into 8th year of treatment	730 days
3-year PI (6th, 7th and 8th year)	Total expulsion	Date, when expulsion was discovered – Date of Day 1 Year 6 +1
	Partial Expulsion/ Mirena removal	Date of Mirena removal – Date of Day 1 Year 6 +1
	Pregnancy	Date of conception – Date of Day 1 Year 6 +1
	Lost to Follow up	Maximum of (Date Mirena last known in situ – Date of Day 1 Year 6 +1; 1 day)
	Continues into 9th year of treatment	Minimum of (1095 days; Date of EOT visit – Date of Day 1 Year 6 +1)
Overall PI	Total expulsion	Date, when expulsion was discovered –Baseline visit date +1
	Partial Expulsion/ Mirena removal	Date of Mirena removal – Baseline visit date +1
	Pregnancy	Date of conception – Baseline visit date +1
	Lost to Follow up	Maximum of (Date Mirena last known in situ – Baseline visit date +1; 1 day)
	Continued until EOT	Date of EOT visit – Baseline visit date +1

A pregnancy will be allocated to the time period(s) that are relevant for the calculation of the PIs described above, e.g., a pregnancy that occurs on day 400 will be relevant for the 7th year PI, the two years PI (6th and 7th year), the three years PI (6th, 7th and 8th year), and the overall PI. Pregnancies that occur before Day 1 Year 6 of Mirena use will not count for the 1-year PI, 2-year PI and 3-year PI. Pregnancies that occur after the Mirena was removed or an expulsion was realized will not count for any PI.

[…]

Furthermore, it should be noted that pregnancies that occur within 7 days after the end of exposure will count for the PIs.

Exposure times to be subtracted:

Subjects who apply additional concomitant contraception are not in risk or are under a lower risk of getting pregnant than subjects who do not apply additional contraception. In case a subject uses concomitant contraceptive methods (e.g., condoms to prevent STD) the respective 28-day reference period(s) of additional contraceptive method use will be excluded from the exposure time, unless a pregnancy occurred in that 28-day reference period.

[…]

The primary analysis set will be the PAS Year 6 (for the analysis after 6 years), the PAS Year 7 (for the analysis after 7 years) and the PAS Year 8 (for the final analysis after 8 years), respectively. Furthermore, analyses will be repeated for the FAS.

[…]

15.1.2.30 Section 10.3.2.2.1 Menstrual blood loss

This section was changed as a result of Modification 15.1.1.10.

Old text:

[…]

The basis for this analysis is the data on MBL assessed by the alkaline hematin method (see section 9.4.2). If a woman has documented in the eDiary (see section 9.7.1) that no bleeding occurred during one of the ~~considered~~ 30-day time periods for collection of sanitary ~~protection~~, the MBL will be assumed to be zero in that time period.

This analysis will be conducted in the FAS in the subgroup ~~of~~ women who had Mirena inserted for HMB.

New text:

[…]

The basis for this analysis is the data on MBL assessed by the alkaline hematin method (see section 9.4.2). If a woman has documented in the eDiary (see section 9.7.1) that no bleeding occurred during one of the 30-day time periods considered for collection of sanitary products,

the MBL will be assumed to be zero in that time period. The handling of partial or missing data (i.e. data on sanitary products and/or bleeding intensities) and detailed imputation rules will be described in the statistical analysis plan.

This analysis will be conducted in the FAS in the HMB subgroup, i.e. women who had Mirena inserted for both contraception and HMB.

[…]

15.1.2.31 Section 10.3.2.2.2 Categorized menstrual blood loss (MBL) (<80ml / 30 days)

This section was changed as a result of Modification 15.1.1.11.

Old text:

No clinical change in bleeding profile regarding HMB will be concluded if the volume of blood loss ~~remains~~ < 80mL ~~during~~ the end of years 6, 7 and 8. Therefore, the proportion of women with ~~an MBL <80 mL / 30 days will~~ analyzed. Descriptive statistics as well as 95% Clopper-Pearson confidence intervals will be provided ~~for each of the time periods in which HMB is assessed.~~ Success will be concluded regarding this endpoint if less than 20% of the women ~~included into the study for HMB~~ have a clinical change in bleeding profile (according to the definition above).

This analysis will be conducted in the FAS in the subgroup ~~of~~ women who had Mirena inserted for HMB.

New text:

No clinical change in bleeding profile regarding HMB after Year 5 until the end of Year 6, until the end of Year 7 and until the end of Year 8, respectively, will be concluded if the volume of blood loss was < 80mL at the beginning of Year 6 and remained < 80mL at the end of Years 6, 7 and 8, respectively. Vice versa, clinical change in bleeding profile regarding HMB after Year 5 until the end of Year 6, end of Year 7 and end of Year 8, respectively, will be concluded if the volume of blood loss was ≥ 80mL at the beginning of Year 6 or at end of Years 6, 7 or 8, respectively.

Therefore, the proportion of women with clinical change in bleeding profile regarding HMB will be analyzed. Descriptive statistics as well as 95% Clopper-Pearson confidence intervals will be provided.

For the analysis after 6 years, the proportion of women with clinical change in bleeding profile regarding HMB **after Year 5 until the end of Year 6** will be analyzed.

For the analysis after 6 years, the following women will constitute the denominator:

- Baseline MBL>80mL/30days, or
- Baseline MBL not >80mL/30days and
  End of Year 6 MBL assessment available.

That means, women with Baseline MBL not >80mL/30days and MBL assessment at the end of Year 6 not available will be excluded from the denominator, as they are considered lost to follow up without preceding clinical change in bleeding profile regarding HMB.

For the analysis after 6 years, the following women will constitute the nominator:

- Baseline MBL>80mL/30days, or
- End of Year 6 MBL>80mL/30days.

For the analysis after 7 years, the proportion of women with clinical change in bleeding profile regarding HMB **after Year 5 until the end of Year 7** will be analyzed.

For the analysis after 7 years, the following women will constitute the denominator:

- Baseline MBL>80mL/30days, or
- End of Year 6 MBL>80mL/30days, or
- Baseline MBL not >80mL/30days and
  End of Year 6 MBL not >80mL/30days and
  End of Year 7 MBL assessment available.

That means, women with Baseline MBL not >80mL/30days, MBL at the end of Year 6 not >80mL/30days and MBL assessment at the end of Year 7 not available will be excluded from the denominator, as they are considered lost to follow up without preceding clinical change in bleeding profile regarding HMB.

For the analysis after 7 years, the following women will constitute the nominator:

- Baseline MBL>80mL/30days, or
- End of Year 6 MBL>80mL/30days, or
- End of Year 7 MBL>80mL/30days.

For the final analysis after 8 years, the proportion of women with clinical change in bleeding profile regarding HMB **after Year 5 until the end of Year 8** will be analyzed.

For the analysis after 8 years, the following women will constitute the denominator:

- Baseline MBL>80mL/30days, or
- End of Year 6 MBL>80mL/30days, or
- End of Year 7 MBL>80mL/30days, or
- Baseline MBL not >80mL/30days and
  End of Year 6 MBL not >80mL/30days and
  End of Year 7 MBL not >80mL/30days and
  End of Year 8 MBL assessment available.

That means, women with Baseline MBL not >80mL/30days, MBL at the end of Year 6 not >80mL/30days, MBL at the end of Year 7 not >80mL/30days and MBL assessment at the end of Year 8 not available will be excluded from the denominator, as they are considered lost to follow up without preceding clinical change in bleeding profile regarding HMB.

For the analysis after 8 years, the following women will constitute the nominator:

- Baseline MBL>80mL/30days, or
- End of Year 6 MBL>80mL/30days, or
- End of Year 7 MBL>80mL/30days, or
- End of Year 8 MBL>80mL/30days.

Success will be concluded regarding this endpoint if less than 20% of the women in the HMB subgroup have a clinical change in bleeding profile regarding HMB (according to the definition above) and the upper limit of the corresponding 95% Clopper-Pearson confidence interval is equal to or less than 35%.

This analysis will be conducted in the FAS in the HMB subgroup, i.e. women who had Mirena inserted for both contraception and HMB.

15.1.2.32 Section 10.3.2.3 Analysis of safety variables

This section was changed as a result of Modification 15.1.1.15 and 15.1.1.26.

Old text:

All safety variables will be analyzed based on the SAF.

The main safety variable is the incidence of ~~post-baseline~~ adverse events (both serious and non-serious).

New text:

All safety variables will be analyzed based on the SAF.

The main safety variable is the incidence of treatment-emergent adverse events (both serious and non-serious). Treatment-emergent AEs are defined as any AEs occurring during the 'extension treatment period' starting at Day 1 of Year 6 of Mirena use.

15.1.2.33 Section 10.3.2.3.2 Bleeding pattern

This section was changed as a result of Modification 15.1.1.10, 15.1.1.19 and 15.1.1.26.

Old text:

Bleeding diary data will be analyzed according to the sponsor's Best ~~p~~practice entitled "Recording and evaluation of bleeding data".

[…]

Table 10–2 Bleeding Intensity Codes and WHO Definitions for Bleeding Intensity

Bleeding Intensity Codes	WHO Definitions	
~~3~~ - 5	Bleeding/spotting episode:	Day(s) with bleeding/spotting preceded and followed by at least 2 bleeding-free days.
2	Spotting-only episode:	Day(s) with spotting preceded and followed by at least 2 bleeding-free days.
1	Bleeding/spotting-free interval:	At least 2 days without bleeding/spotting preceded and followed by at least 1 bleeding/spotting day.

[…]

Based on daily data obtained from the electronic diary, the bleeding pattern will be reported using reference periods of 28 and 90 days. The first 28-day and 90-day reference period, respectively, will start at ~~the baseline visit (Visit 2)~~. For each subject and for each period, the number of bleeding/spotting days and bleeding/spotting episodes will be calculated.[…]

New text:

Bleeding diary data during the 'extension treatment period' starting at Day 1 of Year 6 of Mirena use will be analyzed according to the sponsor's Best Practice Document entitled "Recording and evaluation of bleeding data". Bleeding diary data prior to the 'extension treatment period' will not be included in the analyses. The handling of partial or missing data and detailed imputation rules will be described in the statistical analysis plan.

[…]

Table 10–2 Bleeding Intensity Codes and WHO Definitions for Bleeding Intensity – amended

Bleeding Intensity Codes	WHO Definitions	
2 - 5	Bleeding/spotting episode:	Day(s) with bleeding/spotting preceded and followed by at least 2 bleeding-free days.
2	Spotting-only episode:	Day(s) with spotting preceded and followed by at least 2 bleeding-free days.
1	Bleeding/spotting-free interval:	At least 2 days without bleeding/spotting preceded and followed by at least 1 bleeding/spotting day.

[…]

Based on daily data obtained from the electronic diary, the bleeding pattern will be reported using reference periods of 28 and 90 days. The first 28-day and 90-day reference period,

respectively, will start at Day 1 of Year 6 of Mirena use. For each subject and for each period, the number of bleeding/spotting days and bleeding/spotting episodes will be calculated. […]

15.1.2.34 Section 10.5 Planned interim analyses

This section was changed as a result of Modification 15.1.1.1.

Old text:

No formal interim analysis in the sense of a group sequential or adaptive design is planned. However, an analysis of the data is planned after ~~y~~ear 7, including all subjects who have prematurely discontinued or completed Visit 6, i.e. treated with Mirena for up to 7 years (2 years in the study).

New text:

No formal interim analysis in the sense of a group sequential or adaptive design is planned. However, an analysis of the data is planned after Year 6, including all subjects who have prematurely discontinued or completed Visit 4, i.e. treated with Mirena for up to 6 years (1 year in the study). Another analysis of the data is planned after Year 7, including all subjects who have prematurely discontinued or completed Visit 6, i.e. treated with Mirena for up to 7 years (2 years in the study).

15.1.2.35 Section 11.1 Data recording

This section was changed as a result of Modification 15.1.1.23.

Old text:

The data collection tool for this study will be eCRF; a validated electronic data capture system called RAVE. Subject data necessary for analysis and reporting will be entered/transmitted into a validated database or data system (CIE/TOSCA; SAS).

~~Covance will perform the data entry for this study.~~ Data will be entered by site personnel into an internet based electronic data capture software system RAVE, which Covance has licensed from Medidata Solutions Worldwide. RAVE has been validated by Medidata Solutions Worldwide and Covance for use in its clinical studies. […]

New text:

The data collection tool for this study will be eCRF; a validated electronic data capture system called RAVE. Subject data necessary for analysis and reporting will be entered/transmitted into a validated database or data system (e.g. CIE/TOSCA; SAS).

Data will be entered by site personnel into an internet based electronic data capture software system RAVE, which Covance has licensed from Medidata Solutions Worldwide. RAVE has

been validated by Medidata Solutions Worldwide and Covance for use in its clinical studies. […]

15.1.2.36 Section 13.1 Investigators and other study personnel

New text added:

The name and contact information for the Sponsor's Study Medical Expert is provided in Section 1. The co-ordinating investigator who will be responsible for signing the CSR, is PPD (study center #PPD All other study personnel not included in this section are identified in a separate personnel list (not part of this clinical study protocol) as appropriate. […]

15.1.2.37 Section 14 Reference list

This section was changed as a result of Modification 15.1.1.20.

Old text:

1. Rowe P, Farley T, Peregoudov A, Piaggio G, Boccard S, Landoulsi S, Meirik O; IUD Research Group of the UNDP/UNFPA/WHO/World Bank Special Programme of Research; Development and Research Training in Human Reproduction. Safety and efficacy in parous women of a 52-mg levonorgestrel-medicated intrauterine device: a 7-year randomized comparative study with the TCu380A. Contraception. 2016 Jun;93(6):498-506. doi: 10.1016/j.contraception.2016.02.024. Epub 2016 Feb 23.
2. Sivin I, Stern J, Coutinho E, Mattos CER, El Mahgoub S, Diaz S et al. Prolonged intrauterine contraception: a seven-year randomized study of the levonorgestrel 20 mcg/day (LNG 20) and the Copper T380 Ag IUDS. Contraception 1991;44:473-80.

New text:

1. McNicholas C, Swor E, Wan L, Peipert JF. Prolonged use of the etonogestrel implant and levonorgestrel intrauterine device: 2 years beyond Food and Drug Administration-approved duration. Am J Obstet Gynecol. 2017 Jan 29[Epub ahead of print].
2. Rowe P, Farley T, Peregoudov A, Piaggio G, Boccard S, Landoulsi S, Meirik O; IUD Research Group of the UNDP/UNFPA/WHO/World Bank Special Programme of Research; Development and Research Training in Human Reproduction. Safety and efficacy in parous women of a 52-mg levonorgestrel-medicated intrauterine device: a 7-year randomized comparative study with the TCu380A. Contraception. 2016 Jun;93(6):498-506. doi: 10.1016/j.contraception.2016.02.024. Epub 2016 Feb 23.
3. Sivin I, Stern J, Coutinho E, Mattos CER, El Mahgoub S, Diaz S et al. Prolonged intrauterine contraception: a seven-year randomized study of the levonorgestrel 20 mcg/day (LNG 20) and the Copper T380 Ag IUDS. Contraception 1991;44:473-80.